TO DETERMINE THE EFFECT OF DEXMEDETOMIDINE IN ATTENUATING ARTERIAL PRESSURE INCREASE DURING LAPAROSCOPIC CHOLECYSTECTOMY

Dissertation submitted

In partial fulfillment for the award of

M.D DEGREE EXAMINATION

M.D ANESTHESIOLOGY & CRITICAL CARE-BRANCH X

KILPAUK MEDICAL COLLEGE & HOSPITAL

CHENNAI-10

SUBMITTED TO

THE TAMILNADU DR.MGR MEDICAL UNIVERSITY

CHENNAI-32

APRIL-2013

CERTIFICATE

This is to certify that this dissertation titled "TO DETERMINE THE EFFECT OF DEXMEDETOMIDINE IN ATTENUATING ARTERIAL PRESSURE INCREASE DURING LAPAROSCOPIC CHOLECYSTECTOMY" has been prepared by **DR. V.SANTHOSH** under my supervision in the Department of Anesthesiology, Government Kilpauk Medical College, Chennai-10 during the academic period 2010-2013 and is being submitted to the Tamil Nadu Dr.MGR Medical University, Chennai-32 in partial fulfillment of the University regulation for the award of Degree of Doctor of Medicine (M.D Anesthesiology) and his dissertation is a bonafide work.

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DECLARATION

I, **DR. V.SANTHOSH**, solemnly declare that the dissertation, "TO DETERMINE THE EFFECT OF DEXMEDETOMIDINE IN ATTENUATING ARTERIAL PRESSURE INCREASE DURING LAPAROSCOPIC CHOLECYSTECTOMY" is a bonafide work done by me in the Department of Anesthesiology and Critical care, Government Kilpauk Medical College, Chennai-10 under the guidance of **PROF.S.GUNASEKARAN, M.D.,D.A.,DNB** Professor and HOD, Department of Anesthesiology, Government Kilpauk Medical College, Chennai-10.

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Date: (V.SANTHOSH)

ACKNOWLEDGEMENT

I wish to express my sincere thanks to **Dr. P. Ramakrishnan, M.D.(Biochem), D.L.O.,** Dean, Government Kilpauk Medical College, Chennai-10 for having kindly permitted me to utilize the facilities of the hospital for the conduct of the study.

I am grateful to the Professor and Head of the Department of Anesthesiology, Kilpauk Medical College and Hospital **Prof. S.Gunasekaran M.D.,D.A.,DNB** for his motivation, valuable suggestions, and constant supervision and for providing all necessary arrangement for conducting the study.

I express my sincere thanks to **Prof. Vasanthi Vidyasagaran M.D.,D.A, DNB**, former Professor & HOD, Department of Anesthesiology, KMC/GRH, for her valuable suggestions and supervision.

I sincerely thank **Prof.P.S.Shanmugham, MD., DA.,** former Professor &HOD, Department of Anesthesiology, KMCH, for his valuable suggestions and constant support.

I also thank my other professors **Prof.S.Soundarapandiyan, MD., DA.,** Professor of Anesthesiology Department, KMCH, **Prof.T. Murugan MD., DA.,** Professor of Anesthesiology Department, GRH, **Prof. R.Lakshmi, MD., DA.,** Professor of Anesthesiology Department, KMCH

and **Prof.G.R.Rajashree, MD**., Professor of Anesthesiology Department, KMCH for their guidance and encouragement in carrying out this study.

I thank the Department of General Surgery and Surgical Gasteroenterology, KMCH & GRH and their faculty members for their kind cooperation and permitting me to use the hospital facilities for the study.

I thank all the Assistant Professors and tutors of Anesthesiology KMCH and GRH for their keen interest and support without which this study would not have been possible.

I sincerely thank Tamilnadu Dr.M.G.R Medical University for giving financial assistance for my study.

I also thank my fellow Postgraduates for supporting me throughout the study. I also thank the theatre personnel for their co-operation and assistance. I also thank my family members for their constant encouragement and help throughout the study.

I wish to thank all the patients whose willingness and patience made this study possible.

I also thank Bharat scans for allowing me to use their lab for performing noradrenaline assay in my study in subsidised rate.

I finally thank God Almighty for his blessings to successfully complete the study.

CONTENTS

ABSTRACT

AIM OF THE STUDY

To study the effect of dexmedetomidine in attenuating the arterial pressure increase due to pneumoperitoneum in patients posted for elective laparoscopic cholecystectomy

AUTHOR : Prof.S.Gunasekaran,M.D.,D.A.,DNB

BACKGROUND

Dexmedetomidine is a alpha 2 adrenoreceptor agoinst being increasingly used in anaesthesia and critical care as they not only decrease the sympathetic tone and attenuate the stress responses to anesthesia and surgery, but also causes sedation and analgesia. Already Clonidine, a similar alpha 2 agonist was proved in attenuating arterial pressure increase during laproscopic surgeries. So we investigated whether IV dexmedetomidine attenuates the hemodynamic stress response to pneumoperitoneum by changing neurohormonal responses during laproscopic cholecystectomy

MATERIAL AND METHODS

After obtaining ethical committee approval from Govt Kilpauk Medical College, 40 patients with average of 18-60 years undergoing elective laproscopic cholecystectomy are to be randomized into two groups of 20 each. Patients to be premedicated with glycopyrrolate 0.2 mg IM one hour before surgery and fentanyl 2mcg/kg IV before induction. The trachea intubated after induction of anaesthesia with propofol 1.5- 2 mg/kg and vecuronium 0.1 mg/kg. Anaesthesia maintained with 1-1.5% sevoflurane and 2:4 O2/N2O at 6lit/min. After induction study group to receive IV dexmedetomidine 0.5 mcg/kg bolus followed by 0.5μg/kg/hr infusion and control group to receive normal saline at same infusion rate. After completion of surgery, pneumoperitoneum deflated slowly and after the patient had adequate respiratory attempts patient reversed with glycopyrrolate and neostigmine IV.

Arterial pressure and heart rate are measured before induction, pre pneumoperitoneum, at pneumoperitoneum(P0), at 5 min , 10 min, 20 min, 30 min

after pneumoperitoneum and post surgery.Serum noradrenaline samples are taken pre pneumperitoneum and at 10 minute pneumoperitoneum.

RESULTS

We observed, that the systolic, diastolic and mean arterial pressure increased abruptly after induction of pneumoperitoneum and this response sustained during the entire pneumoperitoneum period in the control group(group A). In the dexmedetomidine group(group B) hemodynamic responses to the induction of pneumoperitoneum were effectively blunted and the heart rate and blood pressure levels when compared to the control group(group A). In the control group (group A) the 10 minute serum noradrenaline values were significantly higher than the pre pneumoperitoneal values suggesting that all these hemodynamic changes are due to release of catecholamines. In the study group (group B), the noradrenaline levels taken 10 minutes after induction of pneumoperitoneum were significantly not increased when compared with the pre pneumoperitoneal values suggesting that dexmedetomidine effectively suppressed the hemodynamic responses by its central sympatholytic action.

CONCLUSION

We conclude that intravenous administration of dexmedetomidine as an adjunct before induction of pneumoperitoneum in laparoscopic cholecyctectomy effectively attenuates the arterial pressure increase due to pneumoperitoneal response.

INTRODUCTION

Surgical procedures and anaesthetic techniques and gadgets have improved over decades with recent advances and there is drastic fall in the mortality and morbidity. As a result of that there is consequent reduction in health care cost. With the invent of better equipment and modern facilities, along with increased knowledge and better understanding of anatomy, physiology and pathophysiology, has lead to the development of laparoscopy for diagnostic and operative procedures. The pneumoperitoneum and the patient positions required for laparoscopy induce a sequence of pathophysiologic changes in terms of increased intra abdominal pressure (IAP) and systemic CO_2 absorption that can complicate anaesthesia. Hence better understanding of the CO_2 pneumoperitoneum in laparoscopy is important for the anesthesiologist for better management of the patient.

Moreover with the advancements in medical field there is increase in the life expectancy. So as anaesthesiologist, we are expected to anaesthetise elderly patients with associated co morbid conditions, like diabetes, hypertension, Ischemic heart disease etc. So understanding the physiology of CO_2 pneumoperitoneum becomes very much essential.

The multiple benefits like reduced hospital stay, post operative pain, respiratory complications and less cost reported after laparoscopy explains its

increasing use and has now become the standard technique for cholecystectomy. However, the CO_2 pneumoperitoneum required for laparoscopy results in pathophysiologic changes particularly in cardiovascular system and respiratory system like 10-30 % decrease in cardiac output, significant increase in arterial pressure and systemic vascular resistances occurring soon after the beginning of intra abdominal insufflation, with no significant changes in heart rate (HR).Both mechanical and neurohumoral factors contribute to these hemodynamic changes. There is an increase in catecholamines, prostaglandins, renin and vasopressin levels.

There are lots of anaesthetic methods and anaesthetic drugs have been used for attenuating the response associated with pneumoperitoneum. It has been already studied that Clonidine, alpha2-adrenergic agonists effectively attenuates the pneumoperitoneal response of the laparoscopy. Recently, dexmedetomidine is another drug of same family but more specific than Clonidine with better safety profile. We therefore tested the hypothesis, that dexmedetomidine might attenuate the hemodynamic changes induced by increased intra abdominal pressure due to CO_2 pneumoperitoneum by reducing release of noradrenaline.

PATHOPHYSIOLOGY OF CARBON DIOXIDE PNEUMOPERITONEUM

HISTORY OF LAPAROSCOPY

In the year 1901, George Kelling first introduced CO_2 pneumoperitoneum for laparoscopic surgeries. Till 1970s laparoscopy was done only for diagnostic purposes. Later in 1970 therapeutic procedure was started with laparoscopy in gynecology like laparoscopic sterilisation. In 1990s laparoscopy was used for cholecystectomy. With further technical advancement, laparoscopy is used for many abdominal surgeries.

PHYSIOLOGIC EFFECTS:

An important step in all laparoscopy is creation of pneumoperitoneum that is insufflation of gas into the peritoneal cavity for better visualisation of the abdominal contents. Pneumoperitoneum induce both mechanical and physiological changes in various system in the body especially in cardiovascular, respiratory and peripheral vascular system. The systems include

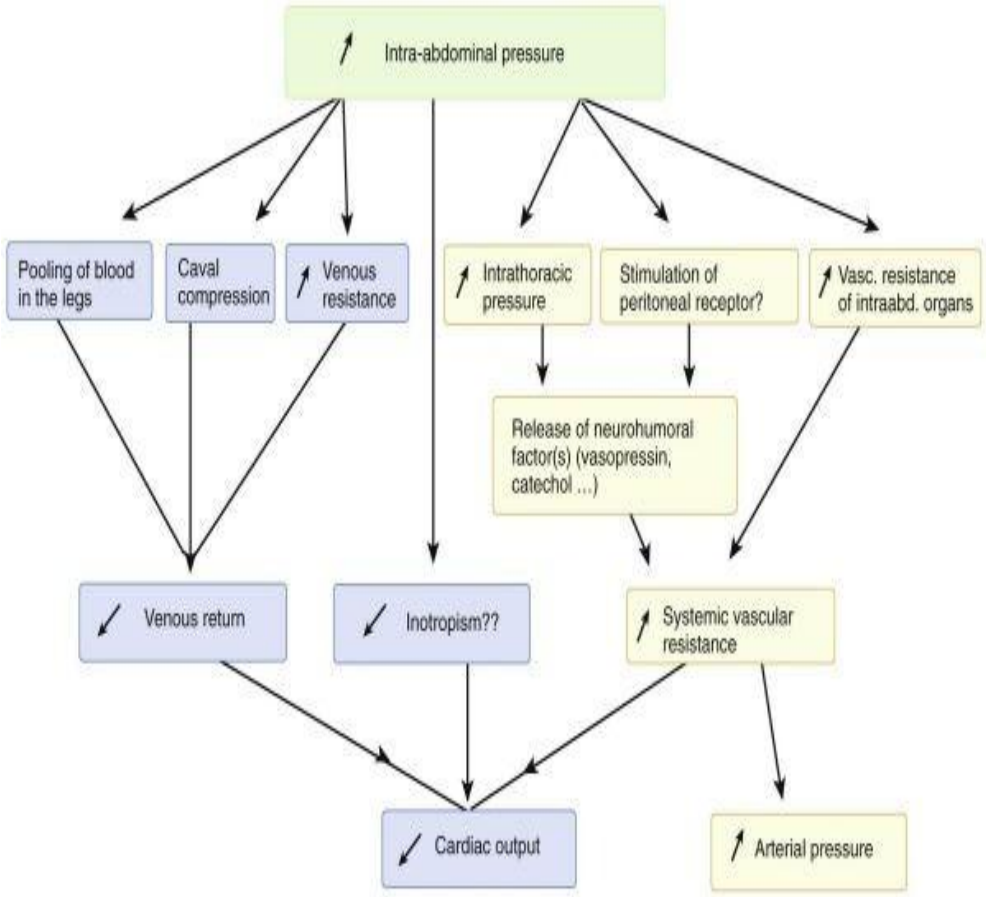
1. •Cardiovascular system
2. • Respiratory system
3. • Renal system
4. • Gastrointestinal system
5. • Peripheral vascular system

CHANGES IN CARDIOVASCULAR SYSTEM

Peritoneal insufflation to IAPs higher than 10 mm Hg induce significant alterations of hemodynamics of the patient. The changes in the cardiovascular system includes decrease in cardiac output, increased arterial pressures, and elevations of systemic and vascular resistances. Heart rates remain unchanged or increased only slightly. The changes in cardiac output either increase or decrease, is proportional to the increase in IAP. These changes might be caused by differences in rates of CO_2 insufflation, IAP, degree of patient tilt, time intervals between insufflation and collection of data, techniques used to assess hemodynamics, and anesthetic techniques. However, most studies have shown a fall of cardiac output (10% to 30%) during peritoneal insufflation whether the patient was placed in the head-down [(1)] or head-up position.[(2)]

The mechanism for decrease in cardiac output is multifactorial. A decrease in venous return is observed after a transient increase in venous return at low IAPs (<10 mm Hg). Increased IAP results in IVC compression, thereby causing venous stasis in the legs, reducing the venous return and preload. Transesophageal echocardiography showed reduction in LVEDV (left ventricular end-diastolic volume) during pneumoperitoneum thereby reasoning the decrease in cardiac output is due to decrease in venous return.[(3)] Cardiac filling pressures, however, rise during peritoneal insufflations is due to increase in intra thoracic pressure accompanying to CO_2 pneumoperitoneum. Hence right

atrial pressure and pulmonary artery occlusion pressure can no longer be considered reliable indices of cardiac filling pressures during pneumoperitoneum. The fact that atrial natriuretic peptide concentrations remain low despite increased pulmonary capillary occlusion pressure during pneumoperitoneum further suggests that abdominal insufflation interferes with venous return.[4] By increasing the circulating volume (preloading) before induction of CO_2 pneumoperitoneum, the decrease in venous return and cardiac output can be attenuated. Increased filling pressures can be achieved by fluid pre loading or slight head-down position of the patient before peritoneal insufflation, by preventing the pooling of blood with intermittent sequential pneumatic compression device or by wrapping the legs with elastic bandages.



The ejection fraction of the left ventricle, assessed by echocardiography, does not appear to decrease significantly when IAP increases to 12 mm Hg. However, all studies describe an increased systemic vascular resistance during the existence of the pneumoperitoneum. This increase in afterload is not due to reflex sympathetic response to decreased cardiac output. Although the normal heart tolerates increases in afterload under physiologic conditions, the increases in afterload produced by the presence of a pneumoperitoneum can be deleterious to cardiac patients.

The increase in systemic vascular resistance is affected by patient position. The Trendelenburg position attenuates this increase;[1] the head-up position aggravates it.[2] The increase in systemic vascular resistance can be corrected by the administration of vasodilating anesthetic agents, such as isoflurane or sevoflurane, or direct acting vasodilating drugs, like nitroglycerin or nicardipine ,or centrally acting sympatholytic drugs like Clonidine.

The increase in systemic vascular resistance is thought to be mediated by mechanical and neurohumoral factors. The alterations in the hemodynamic parameters returns to normal baseline values after several minutes, suggesting involvement of neurohormonal factors. Catecholamines, the renin-angiotensin system, and especially vasopressin are all released during the presence of the CO_2 pneumoperitoneum and may contribute to increasing the afterload.[5] However, only the time course of vasopressin release parallels that of the

increase in systemic vascular resistance.[5] Increases in plasma vasopressin concentrations correlate with changes in intrathoracic pressure and transmural right atrial pressure. Mechanical stimulation of peritoneal receptors also results in increased vasopressin release, systemic vascular resistance, and arterial pressure.[6] However, whether increasing IAP to 14 mm Hg is sufficient to stimulate these mechanical receptors is not clear. The increase in systemic vascular resistance also explains why the arterial pressure increases but the cardiac output falls. Use of α_2-adrenergic agonists such as Clonidine[7] or dexmedetomidine and of β-blocking agents significantly reduces hemodynamic changes and anesthetic requirements. Use of high doses of remifentanil almost completely prevents the hemodynamic changes.

CHANGES IN RESPIRATORY SYSTEM

VENTILATORY CHANGES

CO_2 pneumoperitoneum decreases thoracopulmonary compliance by 30% to 50% in healthy and obese patients.[8] Reduction in functional residual capacity and development of basal atelectasis due to elevation of diaphragm and changes in the distribution of pulmonary ventilation and perfusion from increased airway pressure can be expected. However, increasing IAP to 14 mm Hg with the patient in a 10- to 20-degree head-up or head-down position does

not have significant effect on physiological dead space or shunt fraction in patients without cardiovascular problems.

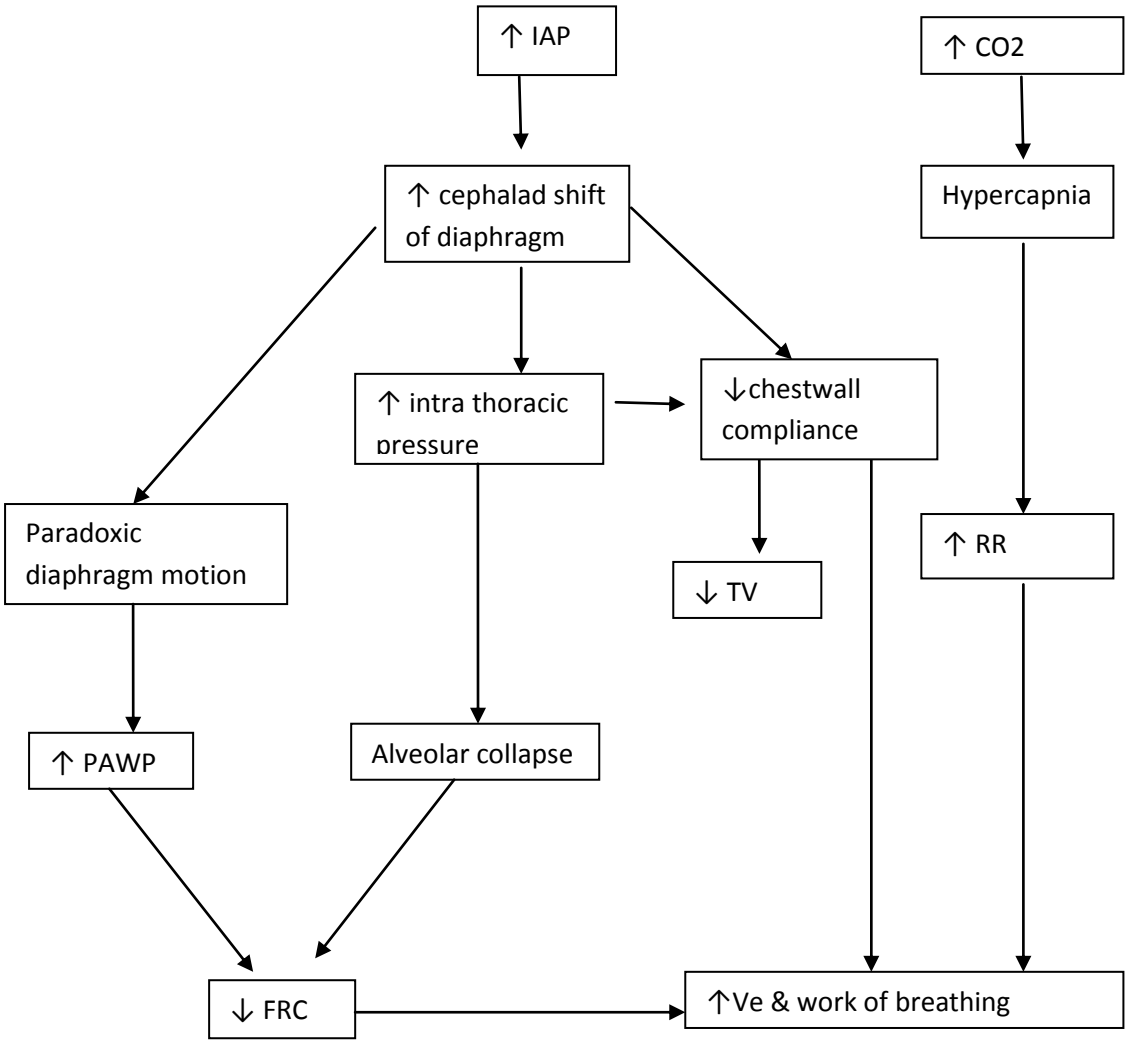
INCREASE IN THE PARTIAL PRESSURE OF ARTERIAL CO2

During uneventful CO_2 pneumoperitoneum, the partial pressure of arterial carbon dioxide (Pa CO_2) progressively increases to reach a plateau 15 to 30 minutes after the beginning of CO_2 insufflation in patients under controlled mechanical ventilation during gynecologic laparoscopy in the Trendelenburg position or during laparoscopic cholecystectomy in the head-up position. After that plateau period any further increase in $PaCO_2$ is independent of or related to CO_2 insufflation and search for other causes such as CO_2 subcutaneous emphysema has to be thought. The increase in Pa CO_2 depends on the IAP. During laparoscopy with local anesthesia, Pa CO_2 remains unchanged but minute ventilation significantly increases due to CO_2. Capnography and pulse oximetry provide reliable monitoring of $PaCO_2$ and arterial oxygen saturation in healthy patients and in the absence of acute intraoperative disturbances.

The increase of $PaCO_2$ is multifactorial and the various reasons attributed are :

- absorption of CO_2 from the peritoneal cavity,
- mechanical compression of the abdominal contents, patient position and controlled ventilation can cause impairment of pulmonary ventilation and perfusion.

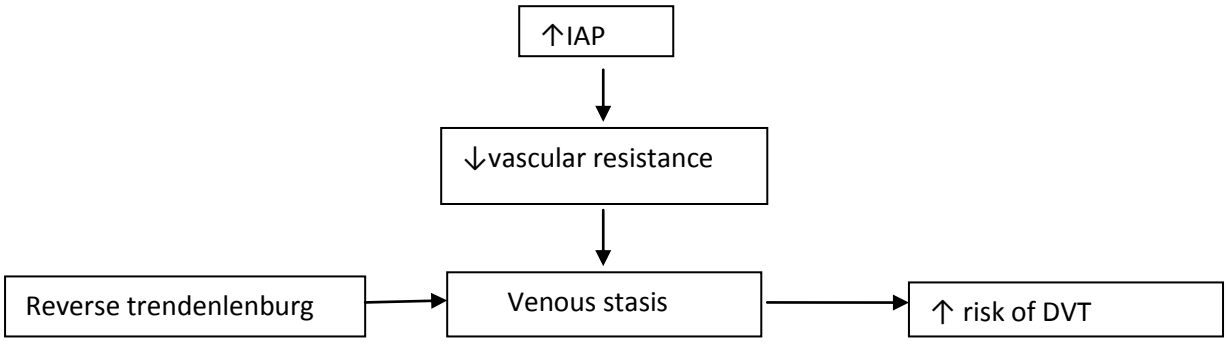
Studies have observed that there is increase in Pa CO_2 levels mainly when CO_2 is used as inflating gas and not when nitrous oxide (N_2O) or helium is used as inflating gas suggesting that the main mechanism of the increased Pa CO_2 during CO_2 pneumoperitoneum is absorption of CO_2 and primarily due to mechanical ventilatory repercussions of increased IAP. [9]



Accordingly, direct measurement of CO_2 elimination V CO_2 using a metabolic monitor combined with investigation of gas exchange showed a 20% to 30% increase of V CO_2 without significant changes in physiologic dead space in healthy patients undergoing pelvic laparoscopy (IAP of 12 to 14 mm Hg) in the head-down position or laparoscopic cholecystectomy in the head-up position. Mismatched ventilation and pulmonary perfusion can result from the position of the patient and from the increased airway pressures associated with abdominal distension.

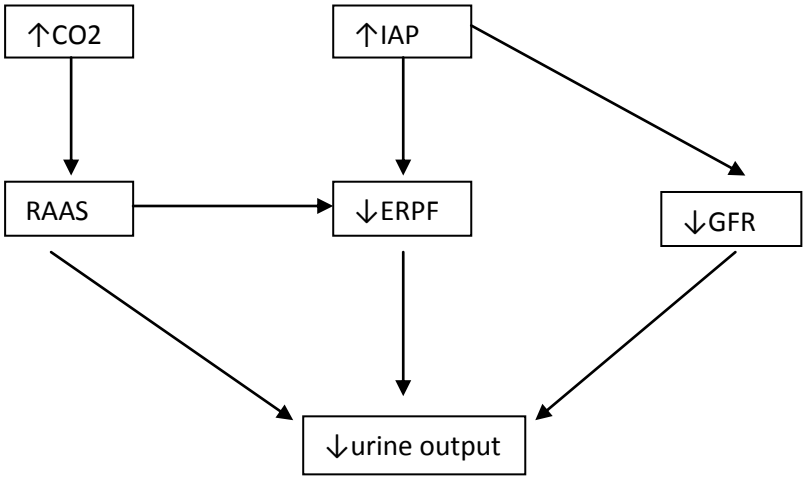
CHANGES IN PERIPHERAL VASCULAR SYSTEM

Increased IAP and the head-up position result in stasis of blood in the lower limbs. Blood flow through femoral vein decreases progressively with increasing IAP, and no adaptation to the reduced femoral venous outflow occurs, even during prolonged procedures thereby predisposing the patient to the development of thromboembolic complications. Although cases of thromboembolism have been reported in the literature, there is no actual increase in incidence during laparoscopy.



CHANGES IN RENAL SYSTEM

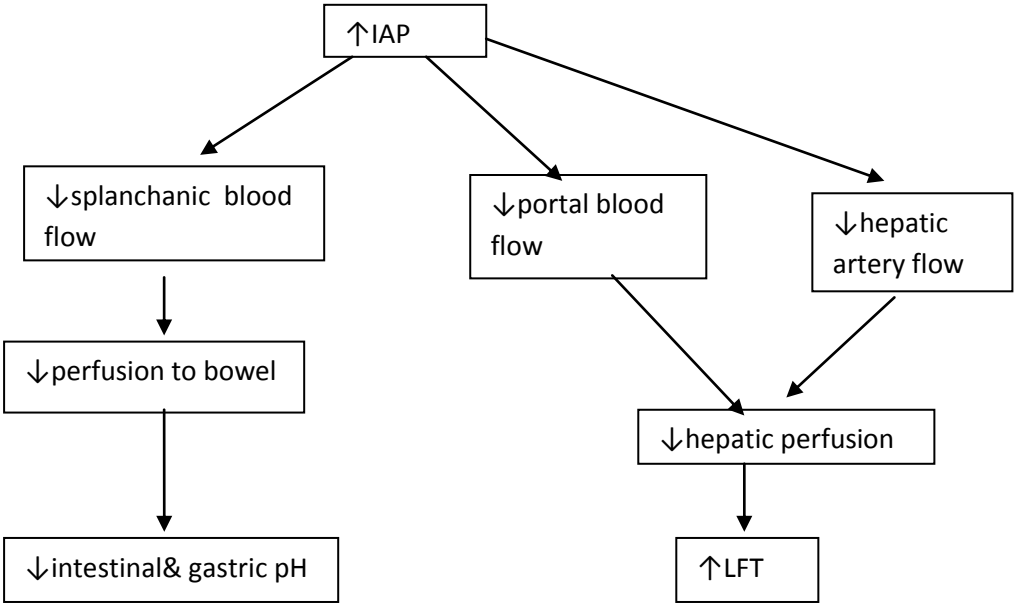
The effect of CO_2 pneumoperitoneum on renal function has also been investigated. During laparoscopic cholecystectomy when compared to open cholecycstectomy there is less than 50% decrease in baseline values of renal plasma flow, glomerular filtration rate and urine output. Urine output significantly increases after deflation.



CHANGES IN HEPATIC SYSTEM

Controversy exists regarding the effect of the CO_2 pneumoperitoneum on splanchnic and hepatic blood flow. A significant reduction was reported in animal and humans. However, others have not observed any significant changes. Blobner and coworkers,[(10)] comparing CO_2 pneumoperitoneum and air pneumoperitoneum in pigs, observed a reduction in splanchnic blood flow during air pneumoperitoneum but not during CO_2 pneumoperitoneum. They

suggest that the direct splanchnic vasodilating effect of CO_2 may counteract the mechanical effect of increased IAP.



CHANGES IN CENTRAL NERVOUS SYSTEM

Cerebral blood flow increases during CO_2 pneumoperitoneum in response to the increased $PaCO_2$.[11]When normocarbia is maintained, pneumoperitoneum combined with the head-down position does not cause any change in intracranial dynamics. Intracranial pressure nevertheless rises during CO_2 pneumoperitoneum, independently of changes in $PaCO_2$, in pigs with preoperative induced intracranial hypertension or normal intracranial pressure and in children with ventriculoperitoneal shunts. Intraocular pressure is not affected by pneumoperitoneum in women with no preexisting eye disease. In an

animal model of glaucoma, pneumoperitoneum only slightly increases intraocular pressure.

POSITION RELATED CHANGES

Patient positioning depends on the surgical site; trendelenburg position is used for pelvic and lower abdominal surgery, reverse trendelenburg position is used for upper abdominal surgery. These positions can cause changes in the hemodynamics that can have effect on the organ system. These positional changes will add up to the changes induced by laparoscopy thereby complicating the clinical scenario. So in laparoscopy, position of the patient definitely have an impact on the following patient hemodynamics.

CARDIOVASCULAR EFFECTS

In clinically normal subjects, the head-down position or the trendelenburg causes an increase in venous return and so preload increases and cardiac output increases. The increase in the cardiac output activates the baroreceptor reflex thus causing vasodilatation and bradycardia. However these changes caused by the position during laparoscopy does not have any significant change in hemodynamics in a normal healthy adult because in general anaesthesia these reflexes are blunted.[2] But these changes can lead to deleterious effects on patients who have poor cardio respiratory reserve.

The Trendelenburg position or the head low position causes passive venous congestion in the cerebral circulation and can cause in elevation of intraocular pressure and this may be deleterious in patients with angle closure glaucoma. But the advantage of this position is that it decreases the intravascular pressure in the lower part of the body like in pelvic organs and reducing the blood loss. But due to decreased intravascular pressure the chances of embolism is increased.

With the head-up position or reverse trendelenburg position, there is a decrease in venous return and thereby cardiac output and the mean arterial pressure decreases. Since pneumoperitoneum induced by laparoscopy also causes decrease in the cardiac output, changes in position will add up these changes. So more the angulations of the head up more will be the fall in cardiac output. This may not have much effect on a normal adult but will have deleterious effects in cardiac patients.

Lithotomy position may aggravate the hemodynamic changes by decreasing the venous return and this may be aggravated in head up position. Because pneumoperitoneum can further cause pooling of blood in the legs, any other factor decreasing the venous return and contributing to circulatory dysfunction should be avoided. Precautions such as supporting the legs, modified lithotomy, adequate padding on the popliteal space, pneumatic

compression decompression device and avoiding tight strapping of legs should be taken.

RESPIRATORY CHANGES

The head-down position or tredenlenburg position can cause lung atelectasis of basal segments. Steep head-down position causes decrease in total lung volume, functional residual capacity and the pulmonary compliance. In healthy patients these changes does not have any major change in hemodynamics and have significant effect on elderly patient or obese patients. The head-up position is considered to be more favourable to respiration.

NERVE INJURY

Head down position with shoulder brace can cause compression of brachial plexus and supraclavicular nerves and can lead to complications. Arms and elbows should be adequately padded and overextension of brachial plexus and ulnar nerve should be avoided. Lower extremity neuropathies and compartment syndromes have been reported after laparoscopy. The common peroneal nerve entrapment is more common in surgeries requiring lithotomy and can be prevented by padding the popliteal region.

ADVANTAGES AND DISADVANTAGES OF LAPAROSCOPY

The advantages include the

- Cosmetic results of small, non–muscle-splitting incisions and scars,
- Decreased blood loss,
- Less postoperative pain and ileus,
- Shorter hospitalization and convalescence, and
- Lower cost.
- Less post operative complications. Wound complications such as infection and dehiscence and incisional hernia are less frequent, and host defence mechanisms may be greater in laparoscopic than in open surgery.

The disadvantages include the

- Laparoscopy is not suitable for patients with poor cardiac reserve and patients with severe respiratory disease,
- Long learning curve for the surgeon (most complications occur during the first 10 laparoscopies),
- The narrowed two-dimensional visual field on video,
- The need for general anesthesia, and the often longer duration.
- Ideally, surgeons should have more advanced laparoscopic skills, especially in knot tying, suturing, and working two instruments simultaneously.
- CO_2 pneumoperitoneum induced hemodynamic complications.

ALTERNATIVES TO CO_2 PNEUMOPERITONEUM

Newer techniques have been investigated to reduce the hemodynamic changes induced by CO_2 pneumoperitoneum in laparoscopy. These include

- Inert gases instead of carbon dioxide
- Gasless laparoscopy

INERT GASES

Insufflation of inert gas like helium or argon instead of CO_2 avoids the increase in $PaCO_2$ and its consequences. [12] And hence hyperventilation is not required, but the ventilatory changes of the increased IAP persist. The hemodynamic changes produced by pneumoperitoneum using inert gas are similar to CO_2 pneumoperitoneum. Unfortunately, the low blood solubility of the inert gases may increase the risk of gas embolism and this safety issue has to investigated.

GASLESS LAPAROSCOPY

Another alternative is gasless laparoscopy. The peritoneal cavity is expanded using abdominal wall lift obtained with a fan retractor. This technique avoids the hemodynamic and respiratory complications of increased IAP and also the consequences of the use of CO_2. Renal and splanchnic perfusion is not altered. Port-site metastases after laparoscopic surgery for cancer are reduced

after gasless laparoscopy. This technique, therefore, is advantages for cardiac and pulmonary disease patients. However, gasless laparoscopy compromises surgical exposure and demands expertise. Combining abdominal wall lifting with low pressure CO_2 pneumoperitoneum (5 mm Hg) may improve surgical conditions.

PHARMACOLOGY OF DEXMEDETOMIDINE

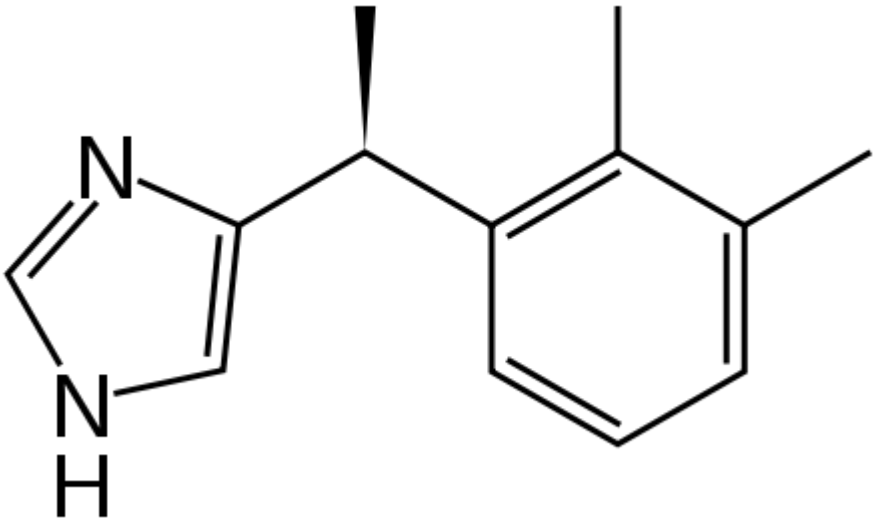
HISTORY

The α_2-adrenergic agonists provide sedation, anxiolysis, hypnosis, analgesia, and sympatholysis. The initial use of α2 agonist in the anaesthesia are made by the observations of Clonidine. This was soon followed by a description of the minimum alveolar concentration (MAC) reduction of halothane by clonidine. Dexmedetomidine is a more selective α_2 agonist than Clonidine. It has $\alpha_{2:}$ α_1 specificity of 1600 : 1 when compared to Clonidine which has 200:1. It was introduced in clinical practice in the United States in 1999 and approved by the FDA only as a short-term (<24 hours) sedative for mechanically ventilated adult ICU patients. Dexmedetomidine is now being used in operation theatres apart from ICU in various settings, including sedation and adjunct analgesia in the operating room, sedation in diagnostic and procedure units, and for other applications such as withdrawal/detoxification amelioration in adult and pediatric patients.

PHYSICOCHEMICAL CHARACTERISTICS

Dexmedetomidine is the d-enantiomer of medetomidine, a substance that has been used for sedation and analgesia in veterinary medicine for many years. The chemical name is (*S*)-4-[1-(2,3-dimethylphenyl)ethyl]-3H-imidazole .

Dexmedetomidine belongs to the imidazole subclass of α_2 receptor agonists, similar to clonidine. It is freely soluble in water.



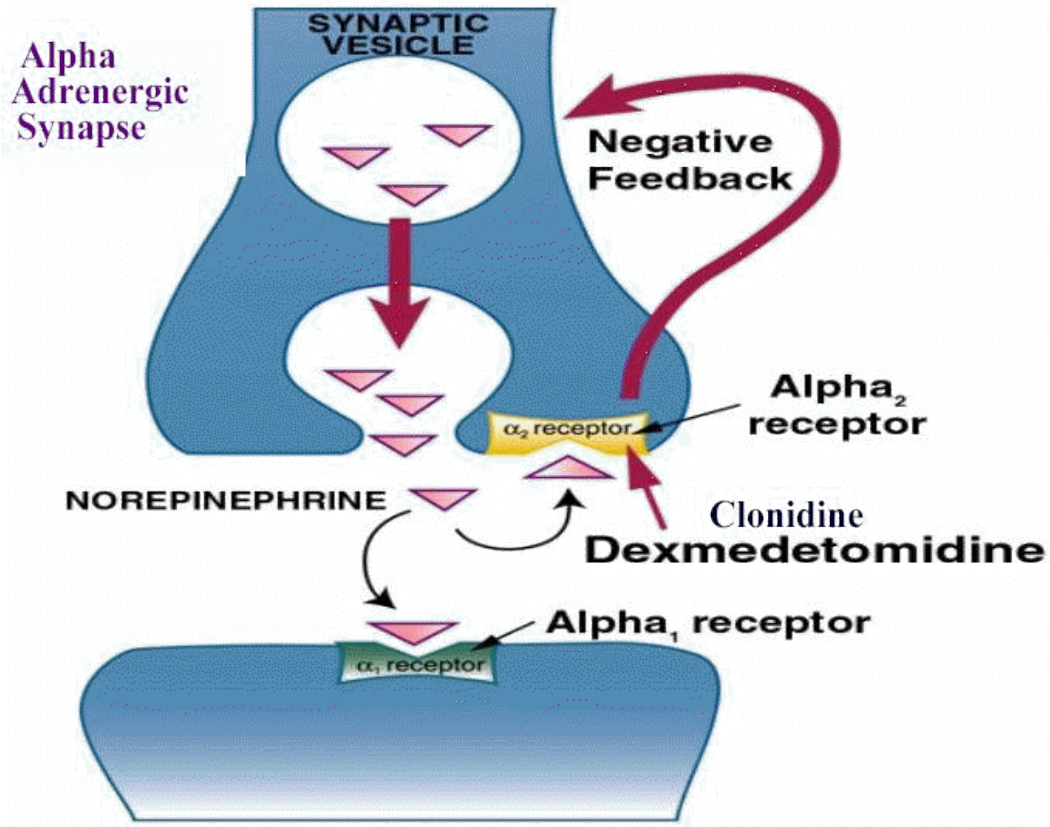
METABOLISM AND PHARMACOKINETICS

Dexmedetomidine has a rapid distribution half life and extensively metabolized in the liver and excreted in urine and feces. The major pathway of metabolism is conjugation (41%) followed by methylation (21%). Dexmedetomidine is 94% protein bound, and its concentration ratio between whole blood and plasma is 0.66. Dexmedetomidine has profound effects on

cardiovascular variables and may alter its own pharmacokinetics. With large doses, there is marked vasoconstriction, which probably reduces the drug's volumes of distribution. In essence, dexmedetomidine displays nonlinear pharmacokinetics. The elimination half-life of dexmedetomidine is 2 to 3 hours, with a context-sensitive half-time ranging from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion. Postoperative patients sedated with dexmedetomidine display similar pharmacokinetics to the pharmacokinetics seen in volunteers.

PHARMACOLOGY

Dexmedetomidine is a nonselective α_2 agonist. Alpha$_2$ adrenoreceptors are membrane-spanning G proteins. Intracellular pathways include inhibition of adenylate cyclase and modulation of ion channels. There are three subtypes of α_2 adrenoreceptors : α_{2A}, α_{2B}, and α_{2C}. In humans the α_{2A} receptors are primarily distributed in the periphery, and α_{2B} and α_{2C} are present in the brain and spinal cord. Postsynaptic located α_2 adrenoreceptors in peripheral blood vessels produce vasoconstriction, whereas presynaptic α_2 adrenoreceptors inhibit the release of norepinephrine, potentially attenuating the vasoconstriction. The overall response to α_2 adrenoreceptors agonists is related to the stimulation of α_2 adrenoreceptors located in the CNS and spinal cord. These receptors are involved in the sympatholysis, sedation, and antinociception effects of α_2 adrenoreceptors.



EFFECTS ON THE CENTRAL NERVOUS SYSTEM

SEDATION

The sedative effect of the α_2 agonists is due to the action on α_2 receptors in the locus caeruleus and an analgesic effect is result of action at α_2 receptors within the locus caeruleus and the spinal cord. [13] The quality of sedation produced by dexmedetomidine seems different compared with that produced by other sedatives acting through the GABA systems. Patients receiving dexmedetomidine infusions as part of their sedation regimen in the postoperative ICU setting have been described as being very easy to wake up and having the ability to follow commands and cooperate while being tracheally

intubated. Undisturbed, patients were noted to fall asleep right away. Dexmedetomidine causes less respiratory depression inspite causing good sedation providing a wide range of safety margin.

The sedative effect is due to action of α_2 agonists through the endogenous sleep-promoting pathways. Dexmedetomidine produces a decrease in activity of the projections of the locus caeruleus to the ventrolateral preoptic nucleus. This increases GABAergic and galanin release in the tuberomammillary nucleus, producing a decrease in histamine release in cortical and subcortical projections. The α_2 agonists seem to inhibit ion conductance through L-type or P-type calcium channels and facilitate conductance through voltage-gated calcium-activated potassium channels. The similarity between natural sleep (non–rapid eye movement) and dexmedetomidine-induced hypnosis has been speculated to maintain cognitive and immunologic function in the sleep-deprived states (as in the ICU).

The α_2 agonists have the advantage that their effects are readily reversible by α_2-adrenergic antagonists (e.g., atipamezole). Atipamezole is not currently approved for human use. Similar to other adrenergic receptors, the α_2 agonists also show tolerance after prolonged administration. Dexmedetomidine can be employed for addiction treatment; dexmedetomidine has been described for use in rapid opioid detoxification, cocaine withdrawal, and iatrogenic induced benzodiazepine and opioid tolerance after prolonged sedation.

ANALGESIA

The analgesic effects of dexmedetomidine are complex. Dexmedetomidine do have an analgesic effect when injected via spinal or epidural. Clonidine injected in the neural axis helps with short-term pain, cancer pain, and neuropathic pain. The effects on blood pressure are slower in onset with an epidural injection than with an intrathecal administration. Epidural effects are seen in 5 to 20 minutes. The primary site of analgesic action is thought to be the spinal cord. Systemic use of dexmedetomidine shows narcotic sparing. There is 50% decrease in the narcotic requirement in ICU patients receiving dexmedetomidine for sedation in the post operative period.

EFFECTS ON THE RESPIRATORY SYSTEM

Dexmedetomidine in sedative doses causes reduction of minute ventilation but the ventilator response to hypercarbia is well maintained. The changes in ventilation appeared similar to those observed during natural sleep. Ebert and colleagues,[14] infusing dexmedetomidine to concentrations of 15 ng/mL in spontaneously breathing volunteers, showed no change in arterial oxygenation or pH. At the highest concentrations, $PaCO_2$ increased by 20%. Respiratory rate increased with increasing concentration from 14 breaths/min to 25 breaths/min. When dexmedetomidine and propofol were titrated to equal sedative end points (BIS of 85), both resulted in no change in respiratory rate. In

a study comparing the effects of remifentanil and dexmedetomidine on respiratory parameters in normal volunteers, the hypercapnic ventilatory response was unaffected even at doses that produced unresponsiveness to vigorous stimulation. $PaCO_2$ increased mildly with dexmedetomidine, but it reached a plateau after the first increment. Dexmedetomidine also exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep and is a safety feature.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

The primary effects of α_2 agonists on the cardiovascular system are reduction in heart rate, systemic vascular resistance; and thereby indirect reduction of myocardial contractility, cardiac output, and systemic blood pressure. By developing highly selective α agonists, it has been hoped to decrease some of these adverse cardiovascular effects and to maximize the desirable hypnotic-analgesic properties. The hemodynamic effects of a bolus dose of dexmedetomidine have shown a biphasic response. After an bolus IV injection of 2 µg/kg of dexmedetomidine, results in an initial increase in blood pressure (22%) and decrease in heart rate (27%) from baseline that occurred at within minutes after induction. The reason for this initial increase of blood pressure is due to the direct vasoconstrictive effect of dexmedetomidine on peripheral α_2 receptors. Heart rate returned to baseline by 15 minutes, and blood pressure gradually declined to approximately 15% below baseline by 1

hour. After an IM injection of the same dose, the initial increase in blood pressure was not seen, and heart rate and blood pressure remained within 10% of baseline.

Ebert and colleagues [14] performed an elegant study in volunteers using a target-controlled infusion system to provide increasing concentrations (0.7 to 15 ng/mL) of dexmedetomidine. The lowest two concentrations produced a decrease in MAP (13%) followed by progressive increase (12%). Increasing concentrations of dexmedetomidine also produce progressive decreases in heart rate (maximum 29%) and cardiac output (35%). Infusion of dexmedetomidine in volunteers also has been shown to result in a compensated reduction in systemic sympathetic tone without changes in baroreflex sensitivity. There is blunted response of heart rate and systemic sympathetic activation owing to sweating, but is less effective in blunting cardiac sympathetic response to shivering.

The incidence of hypotension and bradycardia may be due to loading dose of the drug. This incidence of hypotension and bradycardia can be omitted or reduced by avoiding the bolus dose or not giving more than 0.5 µg/kg. Giving the loading dose over 20 minutes also decreases the incidence of transient hypertension. In several studies after IM and IV administration, dexmedetomidine caused, in a small percentage of patients, profound bradycardia (<40 beats/min) and occasionally sinus arrest/pause. Generally,

these episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergics. It would be expected from its profile that dexmedetomidine would be beneficial to the ischemic myocardium. In animal models, dexmedetomidine showed some beneficial effects on the ischemic heart through decreased oxygen consumption and redistribution of coronary flow from nonischemic zones to ischemic zones after acute brief occlusion. Dexmedetomidine also decreases serum lactate in a dog model of coronary ischemia with an associated decrease in heart rate and measured catecholamines. It also produced an increase in the endocardial/epicardial blood flow ratio by 35%.

The perioperative use of dexmedetomidine reduces the incidence of perioperative myocardial ischemia. More recently, Wallace and associates [15] showed that the administration of clonidine in the preoperative period reduces the incidence of perioperative cardiac ischemia from 31% to 14%, and reduces the mortality for 2 years from 29% to 15% compared with placebo. The only data on potential benefits in perioperative ischemia prevention with dexmedetomidine are provided in an underpowered study in vascular surgery patients who received the drug in the perioperative period. Blood pressure and heart rate were lower in the dexmedetomidine group, but these patients also needed the use of more drugs intraoperatively to sustain blood pressure and heart rate. No reductions of ischemic events were noted. No rebound effects

have been found when discontinuing dexmedetomidine drips, even when it is given for more than 24 hours.

A frequently reported side effect of dexmedetomidine has been a dry mouth. Dry mouth is due to a decrease in saliva production.

USES

Dexmedetomidine has been approved for ICU sedation in patients needing ventilation less than 24 hours. The well documented effects of anxiolysis, sedation, analgesia, and sympatholysis with minimal respiratory depression, makes it an ideal drug and it also has been used in various other clinical scenarios.

INTENSIVE CARE UNIT

Dexmedetomidine has advantages over propofol for sedation of postoperative patients receiving mechanical ventilation. When both drugs were titrated to equal sedation as assessed by the BIS (approximately 50) and Ramsay sedation score (5), dexmedetomidine patients required significantly less narcotics (alfentanil 2.5 mg/hr versus 0.8 mg/hr). Heart rate was slower in the dexmedetomidine group, whereas MAP was similar. In the dexmedetomidine group the Pa_{O_2}/F_{IO_2} ratio was significantly higher. Time to extubation after discontinuation of the infusion was similar at 28 minutes. Patients receiving

dexmedetomidine seemed to have greater recall of their stay in the ICU, but all described this as pleasant overall.

The decreased requirement for opioids (>50%) when dexmedetomidine is used for sedation compared with propofol or benzodiazepines has been confirmed by many studies. Most studies also describe more stable hemodynamics during weaning when dexmedetomidine is used for sedation. This is of obvious benefit in patients with high risk for myocardial ischemia. For sedation in the ICU, loading doses of 0.5 to 1 µg/kg have been used. Infusion rates of 0.1 to 1 µg/kg/hr are generally needed to maintain adequate sedation. Delirium in the ICU is a risk factor for increased length of stay and increased mortality. In a trial of sedation in ventilated patients with dexmedetomidine versus lorazepam, it was found that using dexmedetomidine infusions provided more days alive without delirium or coma and a greater amount of time spent at the appropriate sedation level compared with lorazepam.

Clonidine have been used in the treatment of alcohol and drug withdrawal. In a comparison between clonidine and chlordiazepoxide in the treatment of patients with alcohol withdrawal, clonidine proved to give better anxiolysis with better hemodynamics. Dexmedetomidine has been successfully used in the treatment of -drug withdrawal. Maccioli [16] reported the successful use of dexmedetomidine in two adult patients, one with cocaine and alcohol

withdrawal symptoms, and another with withdrawal from prolonged use of benzodiazepines and narcotics in the ICU. Dexmedetomidine controlled withdrawal behavior and allowed for successful detoxification of young cardiothoracic patients (spanning the ages of days to 17 years) who developed drug withdrawal from prolonged use of benzodiazepines and narcotics in the ICU. Hence dexmedetomidine has been useful in narcotic, alcohol and benzodiazepine withdrawal.

The unique characteristics of dexmedetomidine—providing adequate sedation with minimal respiratory depression—can be used when weaning patients from the ventilator. Siobal and colleagues [17] reported the successful weaning of five ventilated patients who had failed weaning secondary to agitation. Infusions of dexmedetomidine of 0.5 to 0.7 μg/kg/hr were used (no loading) and permitted the discontinuation of propofol in four of five patients. All patients were extubated while still on the dexmedetomidine infusion. One patient required reintubation for upper airway obstruction. The use of dexmedetomidine to facilitate daily "wake up" tests in mechanically ventilated patients seems attractive, but few data have been published.

The FDA approved the use of dexmedetomidine infusions for 24 hours or less. Multiple studies have shown the safety of using this drug for longer periods, however. In data collected from prescribing patterns in 10 institutions, it was shown that dexmedetomidine was used longer than 24 hours in 33.8% of

cases. It also was noted that 33% of patients received a loading dose, 27% of patients received a dose higher than the recommended maximum, and 60% of patients remained on the infusion after extubation.

ANESTHESIA

As a premedicant, dexmedetomidine, at IV doses of 0.5 µg/kg given 15 minutes before surgery, seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia. Within this dosage range, dexmedetomidine reduces thiopental requirements (by ±30%) for short procedures,[18] reduces the requirements of volatile anesthetics (by ±25%), and more effectively attenuates the hemodynamic response to endotracheal intubation compared with 2 µg/kg of fentanyl. Dexmedetomidine also has been evaluated as an IM injection (2.5 µg/kg) with or without fentanyl administered 45 to 90 minutes before surgery. This regimen was compared with IM midazolam plus fentanyl and was found to provide equal anxiolysis, reduced response to intubation, smaller volatile anesthetic requirements, and a decreased incidence of postoperative shivering but a higher incidence of bradycardia. Atipamezole, a selective α_2 antagonist, at 50 µg/kg was effective in reversing the sedation of dexmedetomidine (2 µg/kg intramuscularly), when used to provide sedation for brief operative procedures. This reversal of effects resulted in a more rapid recovery than occurred after equisedative doses of midazolam.

Dexmedetomidine has been used for sedation for monitored anesthesia care. In a study comparing the efficacy of dexmedetomidine or propofol as a sedative agent in a group of 40 patients receiving local anesthesia or regional blocks, dexmedetomidine (1 µg/kg given over 10 minutes) when used for intraoperative sedation resulted in a slower onset than propofol (75 µg/kg/min for 10 minutes), but similar cardiorespiratory effects when titrated to equal sedation. The average infusion rate of dexmedetomidine intraoperatively to maintain a BIS value of 70 to 80 was 0.7µg/kg/min. Sedation was more prolonged after termination of the infusion, as was recovery of blood pressure. Smaller doses of opioid were needed in the first hour, however.

Dexmedetomidine sedation has been done successfully in pediatric patients. Two studies, comprising 140 children 1 to 7 years old, reported successful sedation for MRI scans compared with midazolam or propofol.

When dexmedetomidine is used as a premedication before general surgery for cataract removal, intraocular pressure is decreased (33%), stress hormone secretion is reduced, perioperative narcotic requirements are less, and recovery is more rapid.

For maintenance of anesthesia, dexmedetomidine has been used in patients undergoing multiple types of surgery. In patients given an infusion regimen to achieve a plasma concentration of slightly less than 1 ng/mL,

combined with 70% nitrous oxide, dexmedetomidine reduced isoflurane requirements by 90% compared with a control group. One retrospective study and two prospective, randomized controlled trials in bariatric surgical patients have found that a balanced anesthetic with desflurane or propofol plus dexmedetomidine (0.5 to 0.8µg/kg bolus plus 0.4 µg/kg/hr infusion) reduces postoperative pain scores and morphine consumption, and improves hemodynamics compared with desflurane-fentanyl or propofol-fentanyl anesthetics.

In patients presenting for vascular surgery, three infusion rates of dexmedetomidine were compared with a placebo infusion starting 1 hour before surgery and administered until 48 hours after surgery. In the groups receiving dexmedetomidine, more vasoactive agents were required to maintain hemodynamics intraoperatively, but less tachycardia was noted postoperatively. No other significant differences were noted between the groups.

Grant and colleagues[19] described the use of dexmedetomidine when securing the airway with a fiberoptic intubation in three patients undergoing cervical spine surgery. The procedure was well tolerated with no hemodynamic compromise or respiratory depression. Because this drug provides good sedation with maintainence of respiration, it has been used in patients undergoing awake craniotomies with functional testing and

electrocorticography or awake carotid endarterectomies with fewer fluctuations from the desired sedation level and more stable hemodynamics.

Another use of dexmedetomidine has been as an anesthetic adjunct or sedative agent for patients who are susceptible to narcotic-induced respiratory depression or sleep apnea. This is evident in the use of dexmedetomidine in bariatric surgery. The addition of dexmedetomidine infusions to assist on transesophageal echocardiography examination has been described, with better hemodynamic profile and improved patient satisfaction than with benzodiazepine and narcotics alone, with no added respiratory depression.

The use of dexmedetomidine has dramatically increased. This highly selective α_2 agonist has a set of unique effects that include titratable sedation, sympatholysis, and analgesia without significant respiratory depression. Originally approved as a sedative in the ICU, it has found many off-label applications in the ICU, the operating room, and perioperative environment. The off-label use of dexmedetomidine in infants and children is rapidly increasing. More than 800 reports have been published regarding its use in this population.

VARIOUS ANAESTHETIC TECHNIQUES

FOR LAPAROSCOPIC SURGERY

PREOPERATIVE EVALUATION OF THE PATIENT

Without regard to surgical contraindications, absolute contraindications to laparoscopy and CO_2 pneumoperitoneum are rare, and some still require characterization. Pneumoperitoneum is contraindicated in patients with increased intracranial pressure (e.g., tumor, hydrocephalus, head trauma) and hypovolemia. Laparoscopy can be performed safely in patients with ventricular peritoneal shunt and peritoneojugular shunt that are provided with unidirectional valve resistant to IAPs used during CO_2 pneumoperitoneum.

Cardiac patients coming for laparoscopic surgery, cardiac function should be evaluated because of the hemodynamic changes caused by pneumoperitoneum and patient position can aggravate the present medical situation, particularly in a compromised ventricular function. Patients with severe congestive heart failure and advanced valvular conditions are at increased risk to develop cardiac complications during laparoscopy than patients with ischemic cardiac disease. The choice of laparoscopy verses laparotomy in these patients must be made taking in account, the postoperative

benefits of laparoscopy against the intraoperative risks of laparoscopy. Gasless laparoscopy may represent an alternative for these patients. Because of the side effects of increased IAP on renal function, patients with renal failure deserve special care to optimize hemodynamics during pneumoperitoneum, and the concomitant use of nephrotoxic drugs should be avoided.

In patients with respiratory disease, even though laparoscopy appears superior to laparotomy because of reduced postoperative respiratory dysfunction but in laparoscopy there is increased risk of pneumoperitoneum and risk of ventilation perfusion mismatching. DVT prophylaxis is the same for laparoscopy and laparotomy.

PREMEDICATION

Premedication should be adapted based on the duration of the laparoscopy and to the necessity for quick recovery in daycare setting. All patients undergoing laparoscopy should receive antacid prophylaxis and an anti emetic preoperatively. Preoperative administration of IV paracetemol may be helpful in reducing postoperative pain and opiate requirements.

PATIENT POSITIONING AND MONITORING

Patients must be positioned with great care to prevent nerve injuries; padding should protect from nerve compression at pressure points. The head up or head low position should be done slowly and gradually as sudden change in

position may cause drastic changes in cardiovascular and respiratory system. The patient tilt should be restricted to 15 to 20 degrees. After intubation and postioning the patient, the position of endotracheal tube as to be checked since change in position may cause the tube to move in or move out resulting in accidental endobronchial or extubation respectively. Induction and release of the pneumoperitoneum should be smooth and progressive. Mask ventilation should be as gentle as possible without inflating the stomach, if inflated also ryles tube should be placed and stomach decompressed before trocar placement to avoid gastric perforation specifically in upper abdominal laparoscopy procedures. Emptying of the bladder before all laparoscopic surgeries is must.

RECOMMENDED MANDATORY MONITORING

- Electrocardiography
- Non invasive blood pressure
- Pulse oximetry
- Capnometry and $EtCO_2$
- Temperature
- Invasive monitors like intra arterial blood pressure, central venous pressure, transesophageal echocardiography will be more helpful in case of patients with severe cardiac disease.

ANESTHETIC TECHNIQUES

1. General anaesthesia,
2. Local anaesthesia, and
3. Regional anesthesia

All the three have all been used successfully and safely for laparoscopy.

1. General Anesthesia

General anesthesia with endotracheal intubation and controlled ventilation is certainly the safest and most commonly used technique and therefore is recommended in all patients and for long laparoscopic procedures.

- Choice of induction drugs does not have any role. Either of the induction drugs can be used, propofol, thiopentone or ethiomdate can be used. Profolol induction seems to be associated with lower incidence of post operative complications.
- Although N_2O is not contraindicated in laparoscopic procedures omission of its use seems to cause decreased bowel distention and improve the surgical conditions for intestinal and colonic surgery.
- Adequate analgesia with fentanyl or remifentanyl is required.
- During CO_2 pneumoperitoneum, minute ventilation must be adjusted to maintain P_{ETCO_2} between 30 and 35 mm Hg by adjusting the respiratory

rate rather than tidal volume and this may helpful in COPD patients by preventing barotraumas.

- IAP should be monitored, and kept ideally between 12-15 mm of Hg to reduce hemodynamic and respiratory changes.
- Adequate fluid management minimizes hemodynamic alterations.
- Muscle relaxation should be adequate especially during trocar placement.
- Infusion of vasodilating drugs, such as nitroglycerine, α_2-adrenergic receptor agonists such as Clonidine, and remifentanil reduces the hemodynamic alterations of CO_2 pneumoperitoneum and may facilitate management of cardiac patients.
- Choice of inhalational agents – newer inhalational agents like sevoflurane, isoflurane or desflurane can be safely used.
- All patients should be reversed after adequate breathing attempts with neostigmine and glycopyrrolate and after adequate recovery patient should be shifted with PACU.

The laryngeal mask airway may be an instead of endotracheal intubation even though it does not rule out the risk of gastric aspiration. It allows controlled ventilation and accurate monitoring of P_{ETCO_2}. Since pneumoperitoneum decreases the pulmonary compliance it frequently results in higher airway pressures exceeding 20 cm H_2O only ProSeal laryngeal mask airway which seal upto 30 cm of H_2O can be used in laparoscopy.

Short procedures using low intra abdominal pressure can be done with general anesthesia in patients breathing spontaneously without intubation. It has an advantages over endotracheal intubation that avoids tracheal irritation and use of muscle relaxant. But it is not ideally recommended and its better to use an laryngeal mask airway in these type of patient for short procedures.

2. Local and Regional Anesthesia

It is ideally used for short procedures at day care set up. The advantages of local anaesthesia over general anaesthesia include fast and better recovery, decreased post operative nausea and vomiting, early diagnosis of complications, and fewer hemodynamic changes. Laparoscopic surgeries done under local anaesthesia needs precise and gentle surgical technique and since it is always associated with increased patient anxiety, pain, and discomfort during the surgical manipulation of organs, local anesthesia is always supplemented with intravenous sedation.

Regional anesthesia, both epidural and spinal techniques, combined with the trendelenburg position can be used for gynecologic laparoscopy without major hemodynamic or ventilatory impairment. Laparoscopic cholecystectomy has been successfully performed using epidural anesthesia in COPD patients. The anaesthetic stress of general anaesthesia is reduced by regional anesthesia. Both epidural and local anesthesia have the same benefits and disadvantages.

The advantages of regional anaesthesia include decreased requirement of sedatives, better muscle relaxation than general anaesthesia. The disadvantages being it does not alleviate the discomfort due to abdominal distension and shoulder tip pain due diaphragmatic irritation, and chances are there that the level of block may rise due to increased intra abdominal pressure. Extensive sensory block (T4-L5) is usually necessary for surgical laparoscopy and may also lead to discomfort. The epidural administration of opiates or clonidine, or dexmedetomidine, may help to provide adequate analgesia and decreased hemodynamic response to CO_2 pneumoperitoneum. In case of gaseless laparoscopy regional anaesthesia can provide adequate analgesia.

POSTOPERATIVE MONITORING

Hemodynamic monitoring should be continued in the PACU. The increased systemic vascular resistance, usually last for longer duration even after the release of pneumoperitoneum. After the release of pneumoperitoneum there exists a hyper dynamic circulation due to stagnating blood entering into the central circulation from peripheries, this could lead to adverse events in patients with cardiac disease.

Even though there is decreased pulmonary complications in laparoscopy than laparotomy, PaO_2 still decreases after laparoscopic cholecystectomy. There is an increased oxygen demand in all post laparoscopy patients so it is always

recommended to give supplemental oxygen, even to healthy patients. All patients should be given anti emetic to prevent post operative nausea and vomiting and should be provided adequate analgesia.

PRACTICE GUIDELINES

European Association of Endoscopic Surgery has given guidelines on Pneumoperitoneum for Laparoscopic Surgery.

They have given the monitoring guidelines for normal patients and high risk patients undergoing laparoscopic surgeries.

ASA I/II patients

Pneumoperitoneum of intra abdominal pressure of 12 – 15 mm of Hg rarely causes adverse hemodynamic effects (grade A).

All the basic monitoring are recommended including end tidal CO_2 (grade A).

ASA III/IV

It is advised in all high risk patients to go for alternative of gaseless laparoscopy (grade B)

Even if pneumoperitoneum is indicated IAP should be as low as possible to reduce perfusion changes in renal, hepatic and other organs (grade B).

In all high risk cases, thromboprophylaxis is mandatory (grade A).

Sequential intermittent pneumatic compression of lower extremities is recommended for all prolonged laparoscopic procedures (grade A/B).

In cardiac patients,

- Invasive monitoring is always indicated. Invasive blood pressure and central venous pressure monitoring (grade A)
- Adequate pre-op volume loading +/- B-blockers is recommended (grade A)

In patients with poor respiratory reserve,

- Laparoscopic surgery definitely has better outcome than open method (grade A)
- Intra- and post-op ABG monitoring recommended (grade A)
- Maintaining minute ventilation reduce respiratory acidosis (grade A)

Grade A – strongly recommended and studies have proved it

Grade B – it is advisable and definitely have positive outcome on the patients.

REVIEW OF LITERATURE

STUDIES RELATED TO CO_2 PNEUMOPERITONEAL RESPONSE IN LAPRAROSCOPY

1. Jean L.Moris et al published in American College of cardiology, 1998, the hemodynamic changes induced by laparoscopy and its endocrine correlates and effects of Clonidine on CO_2 pneumoperitoneum. The study conclusion was vasopressin and catecholamines probably mediated the increase in systemic vascular resistance observed during pueumoperitoneum. Clonidine given before pneumoperitoneum reduces the catecholamine release and attenuates hemodynamic changes during laparoscopy.[26]
2. D.Jee et al, published in British Journal of Anaesthesia 2009, the effect of intravenous magnesium sulphate attenuates arterial pressure increase during laproscopic cholcystectomy. They concluded that intravenous magnesium sulphate 50 mg/kg given before pneumoperitoneum attenuated the arterial pressure increase due to pneumperitoneum. This attenuation apparently related to reduction in release of catecholamines and vasopressin or both.[27]
3. K. Myre et al in Acta Anaesthesiologica Scandinavia, march 2003 have studied the effect of high dose remifentanyl(0.39 μg/kg/min) infusion in

attenuating the stress response to pneumoperitoneum in 18 patients undergoing laproscopic fundoplication . The study showed that high dose remifentanyl depressed epinephrine release to pneumoperitoneum.(28)

4. Jens fromholt Larsen et al, in Journal of Gasteroenterolgy surgery 2002, studied the effect of stress response of gasless and carbondioxide pneumoperitoneum. The study showed carbondioxide pneumoperitoneum induced significant change in stress hormones.(29)
5. Gopta.k et al in Saudi Journal of Amaesthesiology 2011, have studied the effect of oral pregabalin (150mg) and oral Clonidine (200µg) for hemodynamic stability during laryngoscpy and laproscopic cholecystectomy and said that both drugs causes anxiolysis and sedation with hemodynamic stability.(30)
6. Tripathi DC et al, in Journal of Anaesthesiology clinical pharmacology October 2011, have studied two different doses of intravenous Clonidine (1µg/kg and 2µg/kg) in attenuating hemodynamic stress response during laparoscopic cholecystectomy. The study concluded that Clonidine 2µg/kg intravenously given 30 minutes before induction is safe and effective preventing hemodynamic stress response during laparoscopy.(31
7. Maharajan SK in Kattmandu University Medical Journal 2005, studied the effect of propanalol in decreasing stress response in laparoscopic cholecystectomy and concluded that propanolol (1 mg intravenous)

effectively blunts the stress response to CO_2 pneumoperitoneum during laparoscopic cholecystectomy.[32]

STUDIES RELATED TO DEXMEDETOMIDINE FOR STRESS ATTENUATION

1. Poonam S.Ghodki et al in journal of Anaesthesiology clinical pharmacology 2012, studied dexmedetomidine as an anaesthetic adjuvant in laproscopic surgery and they concluded dexmedetomidine ia an effective adjunct without the fear of awareness under anaesthesia and resulted in 62.5% reduction in induction dose of propofol and 30% less end tidal isoflurane required. [20]
2. Pekka Talke et al, Department of Anaesthesia, University of California published a paper in Anaesthesia and Analgesia on hemodynamic and adrenergic effects of perioperative effects of dexmedetomidine after vascular surgery. The study showed the group of patients receiving dexmedetomidine infusion had decrease heart rate and plasma nor adrenaline values during emergence from anaesthesia.[21]
3. M. Aho et al in Anaesthesia and Analgesia published an article that intramuscularly given dexmedetomidine of 2.4 μ/kg 45 minutes before surgery attenuated hemodynamic and stress response to gynecologic laparoscopy. [22]

4. H.A.Mowafi et al in British Journal of Anaesthesia, 2008, published the effect of dexmedetomidine premedication on intra ocular pressure changes after scoline and intubation. They showed that dexmedtomidine 0.6μ/kg intravenous resulted in decrease in intraocular and mean arteriolar pressure in the study group. They concluded dexmedetomidine could be a beneficial adjunct in open globe injuries.[23]
5. Ahmed M Muktar et al, Department of medicine, Cairo University studied the use of dexmedetomidine in paediatric cardiac surgery. They concluded dexmedetomidine attenuated increase in heart rate , blood pressure, cortisol and catecholamine concentration in paediatric patients undergoing open heart surgeries.[24]
6. Fredi Menda et al, Department of Anaesthesia, yeditepe university, Turkey, published in annals of cardiac Anaesthesia, about the effect of using dexmedetomidine as an adjunct to attenuate hemodynamic response to endotracheal intubation in patients undergoing Fast trach CABG. The study concluded dexmedetomidine can be safely used to attenuate the hemodynamic response to endotracheal intubation in patients undergoing myocardial revescularisation receiving β blockers.[25]

AIM OF THE STUDY

To study the effect of dexmedetomidine in attenuating the arterial pressure increase due to CO_2 pneumoperitoneum in patients posted for elective laparoscopic cholecystectomy

MATERIALS & METHODS

STUDY DESIGN

It is single blinded randomized study done at Kilpauk Medical College/Government Royapettah Hospital.

PATIENT SELECTION:

40 patients of ASA 1 & 2 of both sex undergoing elective laparoscopic cholecystectomy are selected.

GROUP:

Group A: 20 patients receiving normal saline IV infusion 10 minutes before pneumoperitoneum

Group B: 20 patients receiving IV dexmedetomidine (0.5μ/kg IV bolus followed by IV infusion of 0.5 μ /kg/hr) 10 minutes before pneumoperitoneum

INCLUSION CRITERA

- ASA 1 &2
- 18 to 60 years
- Both sex
- Elective cholecystectomy
- Without any co morbid condition
- Undergoing general anaesthesia

EXCLUSION CRITERIA:

- Patient on any drug treatment which may interfere with dexmedetomidine
- Hypertension
- Diabetes mellitus
- Cardiovascular & kidney disease
- Acute cholecystectomy
- Endocrine or metabolic diseases
- Autonomic neuropathy
- Patients on chronic β blocker therapy

MONITORING:

- Pulse oximetry
- NIBP
- ECG
- Et CO2
- Airway pressure monitoring (PIP and mean pressure)
- Intra abdominal pressure (maintained around 12 mm of Hg)
- Urine output monitoring
- Temperature monitoring

CONDUCT OF STUDY;

After ascertaining the inclusion criteria preoperative investigations were recorded which included complete hemogram, blood sugar, urea, creatinine, serum electrolytes, blood grouping, blood coagulation tests, urine routine, chest X-ray and ECG.

Preoperative instructions:

- All patients are explained about the study and written informed consent obtained.
- Patients are advised a 6 hour period of absolute fasting.
- All patients receive an antacid prophylaxis of injection ranitidine 50 mg IV and injection ondansetron 8 mg IV on the morning of surgery.
- All the patients are premedicated with injection glycopyrrolate 0.2 mg IM one hour before surgery.
- 40 patients are randomized into two groups (group A and group B).

Conduct of anaesthesia:

- After shifting the patients to operation theatre patients are connected to ECG, pulse oximetry, and NIBP monitors.
- All patients are started with ringer lactate at 75 ml/hr.

- All patient given fentanyl 2μg/kg IV and pre oxygenated with 100% oxygen for 3 – 5 minutes.
- In all the patients, trachea was intubated after induction of anaesthesia with propofol 1.5-2 mg/kg and vecuronium 0.1 mg/kg.
- Anaesthesia maintained with 1.5-2% sevoflurane and 4:2 N_2O/O2 at 6 litres/ minute.
- After induction of general anaesthesia and 10 minutes before creation of CO_2 pneumoperitoneum study group (group B) received IV dexmedetomidine 0.5μg/kg bolus dose over 10 minutes followed by 0.5μ/kg/min infusion and control group (group A) received normal saline at same infusion rate. In both the groups infusion was continued till dissection of gall bladder was complete.
- Arterial pressure and heart rate are measured before induction, pre pneumoperitoneum, at pneumoperitoneum(P0), at 5 min , 10 min, 20 min, 30 min after pneumoperitoneum and post surgery.
- **Serum noradrenaline samples are taken pre pneumperitoneum and at 10 minute pneumoperitoneum.**
- After completion of surgery, pneumoperitoneum deflated slowly and after the patient had adequate respiratory attempts patient reversed with glycopyrrolate and neostigmine IV.
- Adequate oral suctioning done and the patients are extubated.

- After adequate recovery from general anaesthesia, patients were shifted to recovery room where they remained and observed until there was complete recovery from general anaesthesia for 2 hours.

Noradrenaline assay

- Serum samples are taken in both plain tube and EDTA tubes and immediately transferred to the laboratory.
- Assay done with ECLIA using Elecsys 2010 system

DEFINITION OF VARIABLES:

- Preoperative values of pulse rate, systolic, diastolic and mean blood pressures were recorded read as outside theatre.
- Patients were preoxygenated and the reading of pulse rate, systolic, diastolic and mean blood pressures were recorded and was read as preoperative.
- Patients were intubated and the reading of pulse rate, systolic, diastolic and mean blood pressures were recorded and was read as prepneumoperitoneum.
- After induction of pneumoperitoneum (intra abdominal pressure reaching 12 mm of Hg) reading of pulse rate, systolic, diastolic and mean blood pressures were recorded and was read as P0.
- From the induction of pneumoperitoneum, pulse rate, systolic, diastolic and mean blood pressures were recorded at 5^{th} minute and was read as P5.
- From the induction of pneumoperitoneum, pulse rate, systolic, diastolic and mean blood pressures were recorded at 10^{th} minute and was read as P10.
- From the induction of pneumoperitoneum, pulse rate, systolic, diastolic and mean blood pressures were recorded at 20^{th} minute and was read as P20.

- From the induction of pneumoperitoneum, pulse rate, systolic, diastolic and mean blood pressures were recorded at 30^{th} minute and was read as P30.
- After completion of the surgery patient extubated and pulse rate, systolic, diastolic and mean blood pressures were recorded and was read as post surgery .

STATISTICAL ANALYSIS:

- It's a randomized controlled clinical study
- Variables were analysed with Student't' test
- Variables like age, sex, weight, height were compared using Levene's test for equality of variance
- Sample size obtained according to previous background study
- 'p' value less than 0.05 was taken as significant

OBSERVATION & RESULTS

In this study a total of 40 patients were studied in which 20 patients in the control (group A) and 20 in the study group (group B). The demographic parameters like age distribution, weight of the patient(kg), height of the patient (cm), and other parameters like duration of anaesthesia, duration of surgery, preoperative pulse rate, systolic, diastolic and mean arterial pressure were compared between the two groups(group A & group B) and there was no statistical difference between the two groups(p □ 0.05).

DEMOGRAPHIC AND OTHER PARAMETERS

VARIABLE	CONTROL (GROUP A)	STUDY (GROUP B)	P VALUE
AGE	48.2 ±5	49.1±4	0.607
SEX M/F	8/12	9/11	0.704
WEIGHT (kg)	77.8±8	70.2±6	0.329
HEIGHT (cm)	163.7±7	165±7	0.509
DURATION OF SURGERY	39.3±4	39.9±4	0.620
DURATION OF ANAESTHESIA	67.5±6	69.2±4	0.340
PREOP PULSE RATE	87.8±10	86.2±4	0.510
PREOP SYSTOLIC BP	107.2±11	102.9±18	0.420
PREOP DIASTOLIC BP	63.6±8	67.3±9	0.205
PREOP MEAN BP	78.1±9	81.9±9	0.220

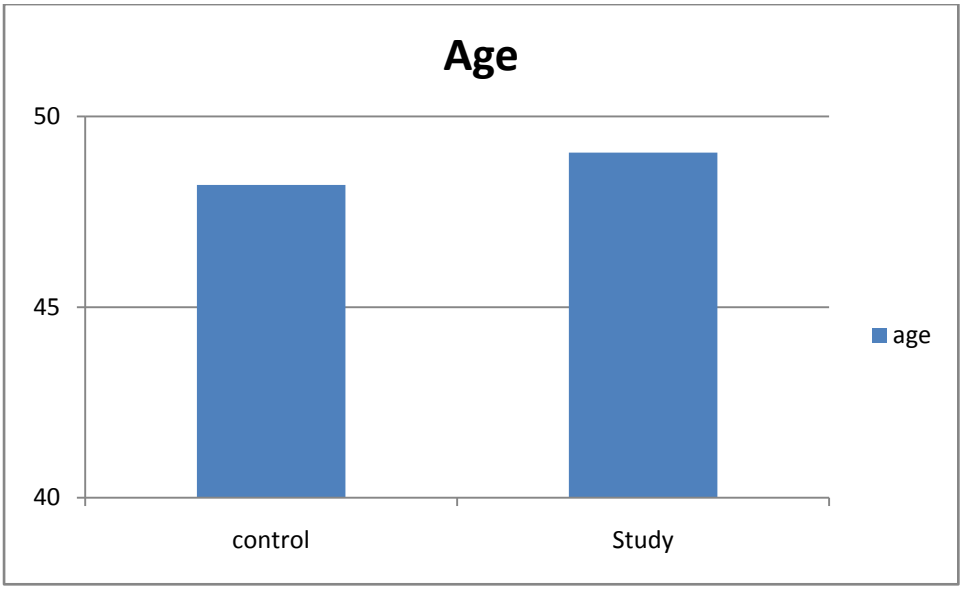


Chart-1 Age distribution between two groups

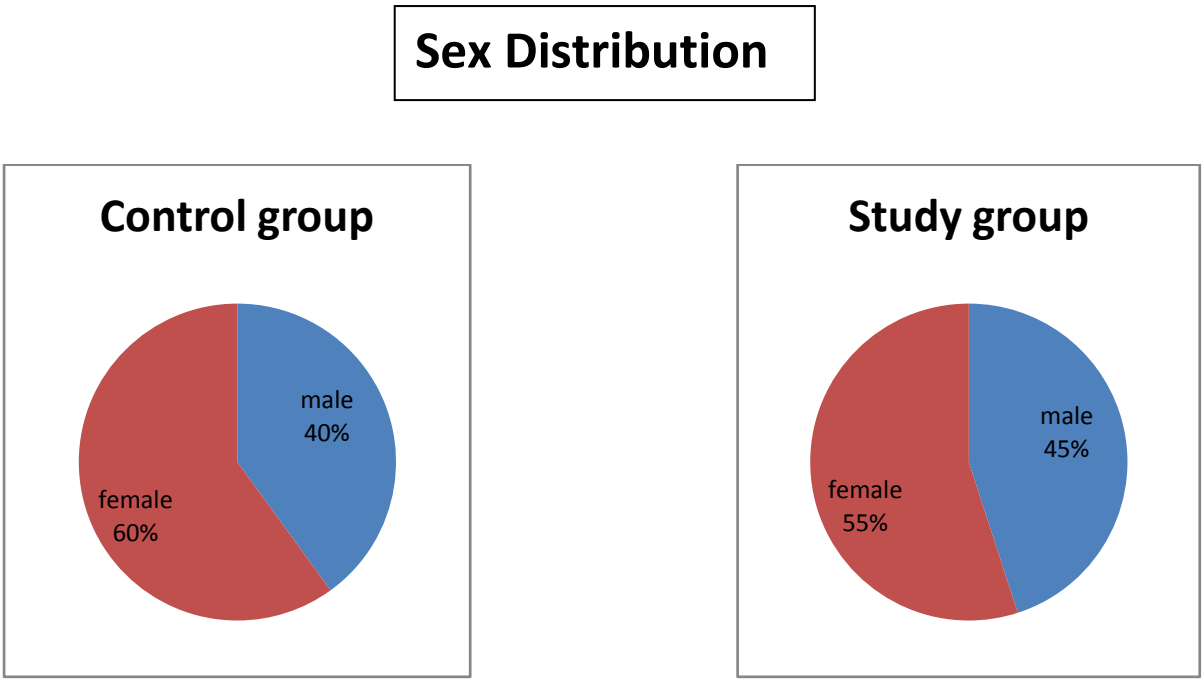


Chart-2 Sex distribution in both groups

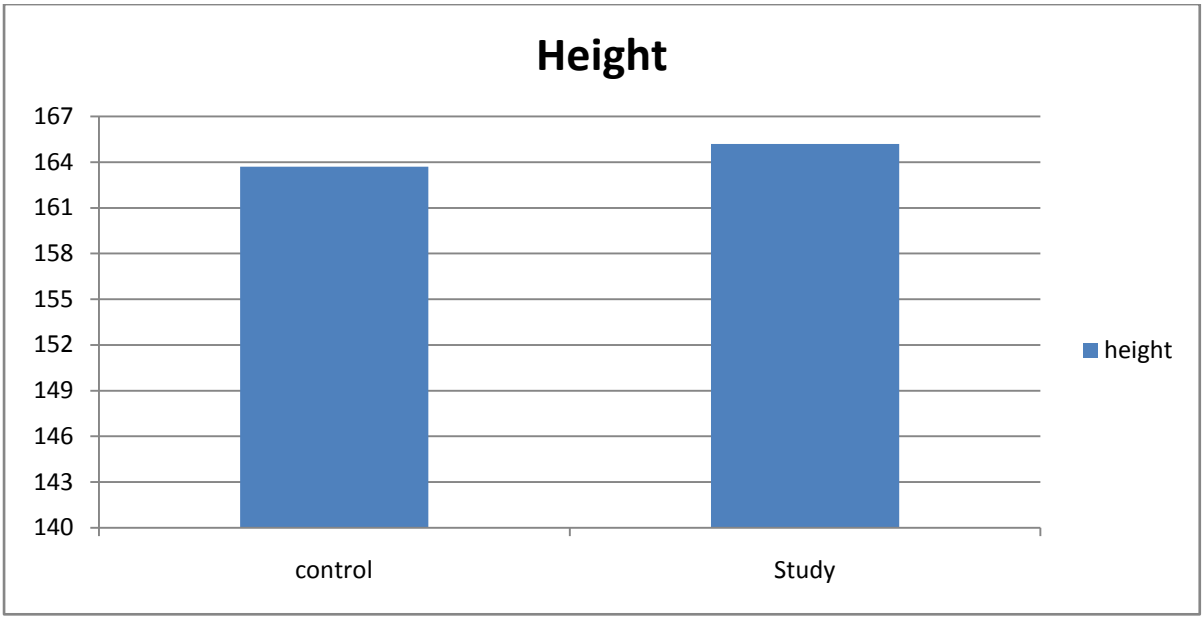


Chart-3 Height (in cms) between both groups

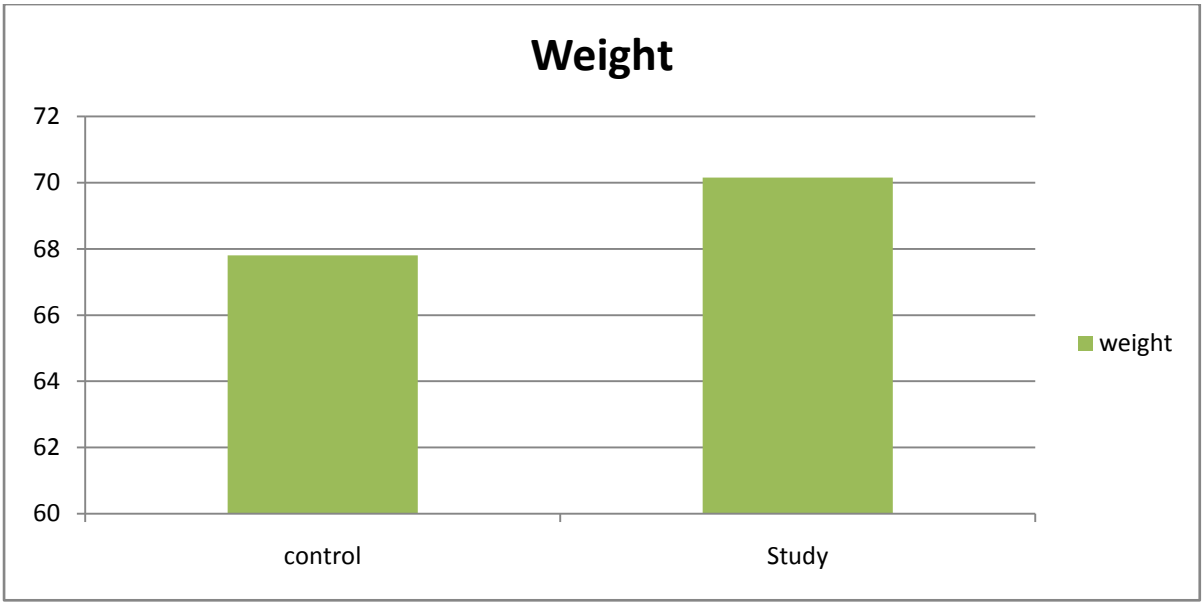


Chart-4 Weight (in kg) between both groups

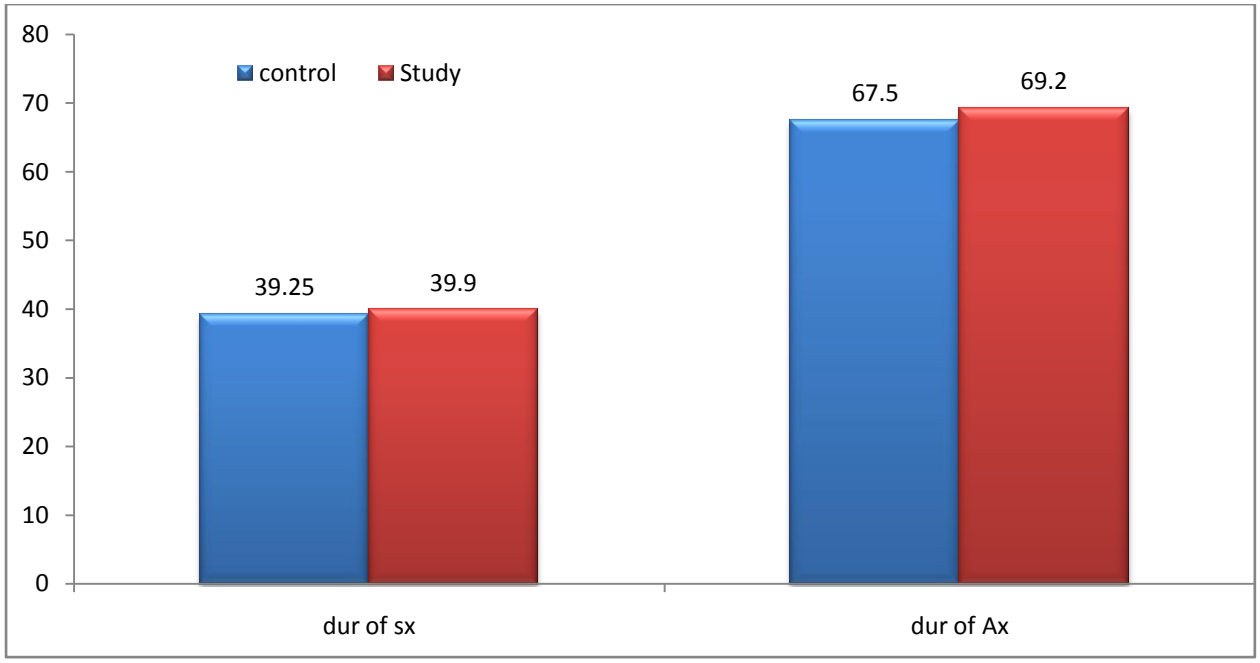


Chart-5 Duration of surgery and duration of anaesthesia are comparable between two groups.

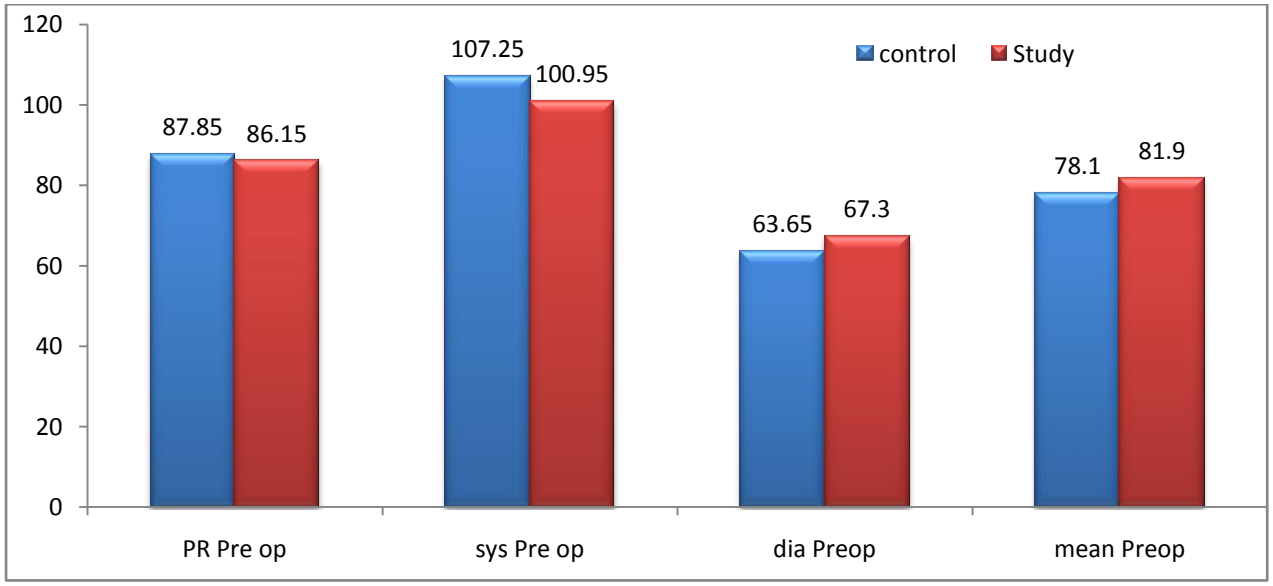


Chart-6 Preoperative pulse rate, systolic, diastolic and mean blood pressure are comparable between two groups.

PULSE RATE

VARIABLE	CONTROL (GROUP A)	STUDY (GROUP B)	P VALUE
MEAN P 0	89.2	77.4	0.000
MEAN P5	85.4	75.0	0.000
MEAN P 10	87.0	73.8	0.000
MEAN P 20	88.0	72.1	0.000
MEAN P 30	84.4	75.2	0.003
MEAN POST SURGERY	88.5	79.6	0.003

P value <0.05 - significant

Test method – student t test

The pulse rate is significantly low in the study group (group B) than the control group (group A) during the period of pneumoperitoneum at 0 min (77 VS 89), 5^{th} min (75 vs 85), 10^{th} min(73 vs 87), 20^{th} min (88 vs72) and 30^{th} min (75 vs 84) and also post surgery (79 vs 88). (chart -7)

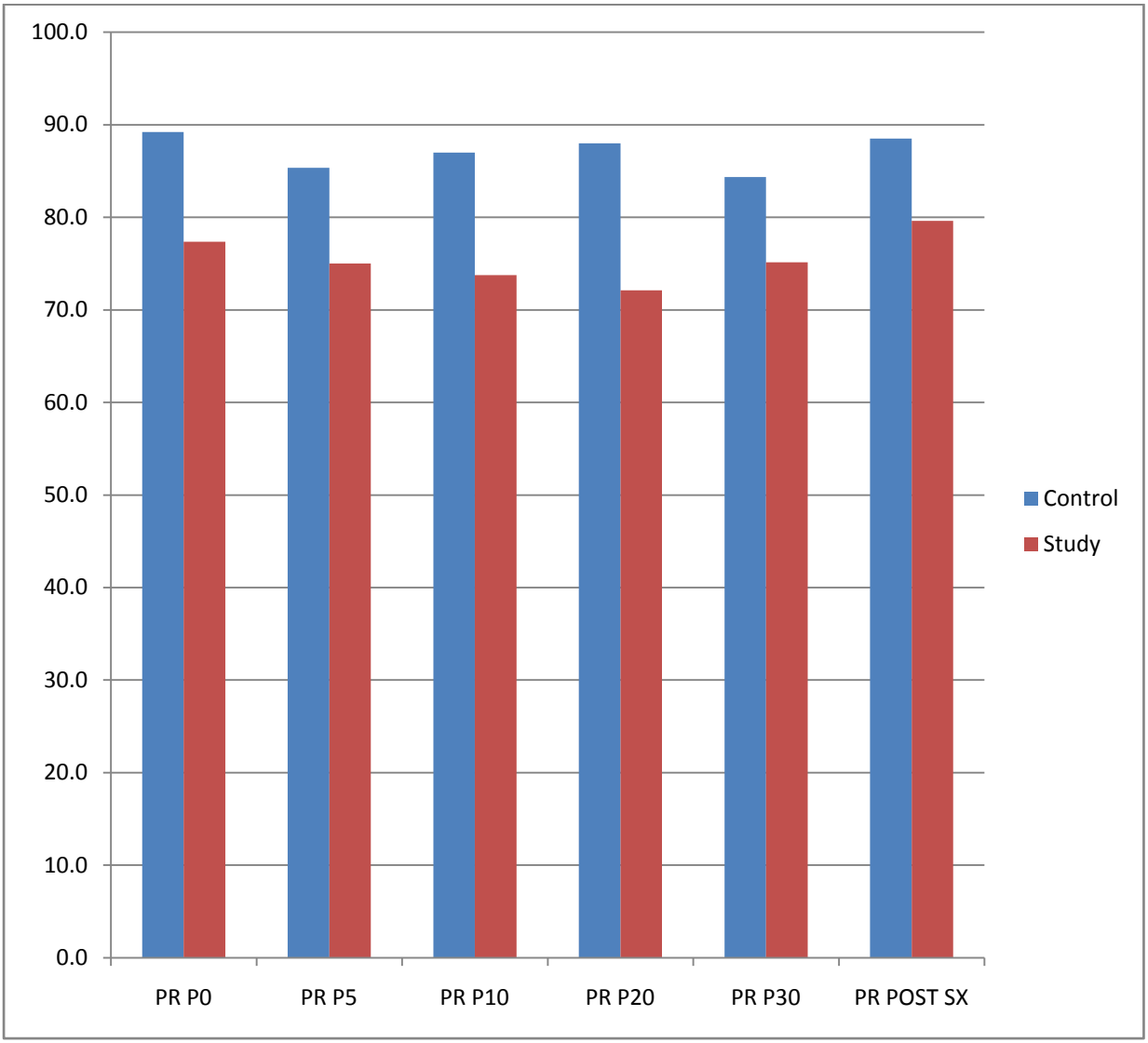


Chart-7 Bar diagram shows heart rate is significantly lower (p value < 0.05) in study group than the control group at all point of time.

SYSTOLIC BLOOD PRESSURE

VARIABLE	CONTROL (GROUP A)	STUDY (GROUP B)	P VALUE
SYSYTOLIC P 0	109.2	103.8	0.003
SYSTOLIC P5	119.3	108.5	0.000
SYSTOLIC P 10	128.3	110.8	0.000
SYSTOLIC P 20	123.9	115.4	0.000
SYSTOLIC P 30	128.5	120.9	0.000
SYSTOLIC POST SURGERY	130.5	123.7	0.001

P value <0.05 - significant

Test method – student t test

The systolic blood pressure is significantly low in the study group (group B) than the control group (group A) during the period of pneumoperitoneum at 0 min (103 vs 109), 5^{th} min (108 vs 119), 10^{th} min(110 vs 128), 20^{th} min (115 vs 123) and 30^{th} min (120 vs 128) and also post surgery(123 vs 130). (chart- 8)

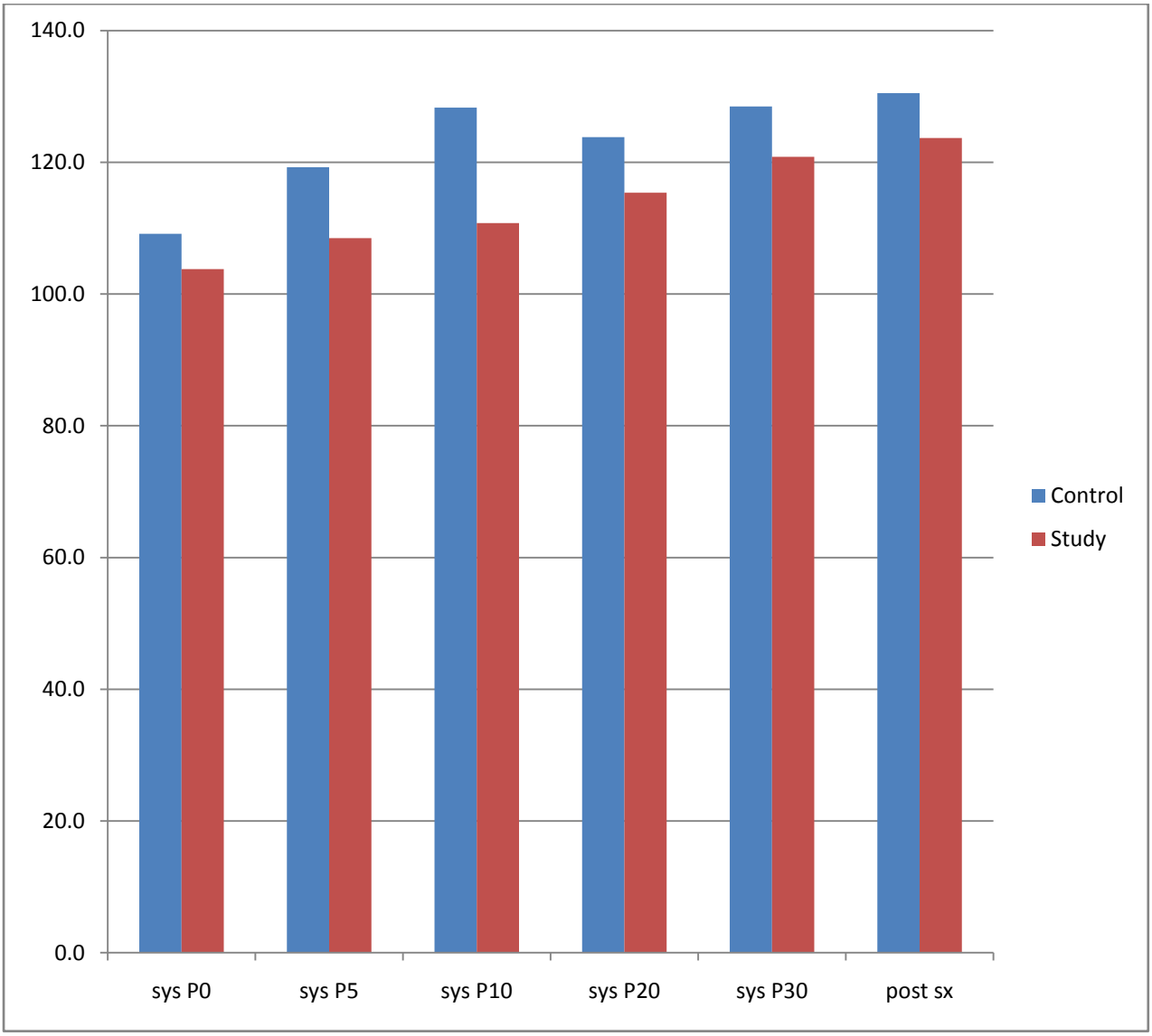


Chart-8 Bar diagram shows systolic blood pressure is significantly lower (p value < 0.05) in study group than the control group at all point of time.

DIASTOLIC BLOOD PRESSURE

VARIABLE	CONTROL (GROUP A)	STUDY (GROUP B)	P VALUE
DIASTOLIC P 0	80.3	75.0	0.000
DIASTOLIC P5	84.2	76.2	0.000
DIASTOLIC P 10	91.3	76.9	0.000
DIASTOLIC P 20	89.8	81.2	0.000
DIASTOLIC P 30	86.9	80.1	0.003
DIASTOLIC POST SURGERY	82.8	74.7	0.001

P value <0.05 - significant

Test method – student t test

The diastolic blood pressure is significantly low in the study group (group B) than the control group (group A) during the period of pneumoperitoneum at 0 min (75 vs 80), 5^{th} min (76 vs 84), 10^{th} min(76 vs 91), 20^{th} min (81 vs 86) and 30^{th} min (80 vs 86) and also post surgery(74 vs 82). (chart-9)

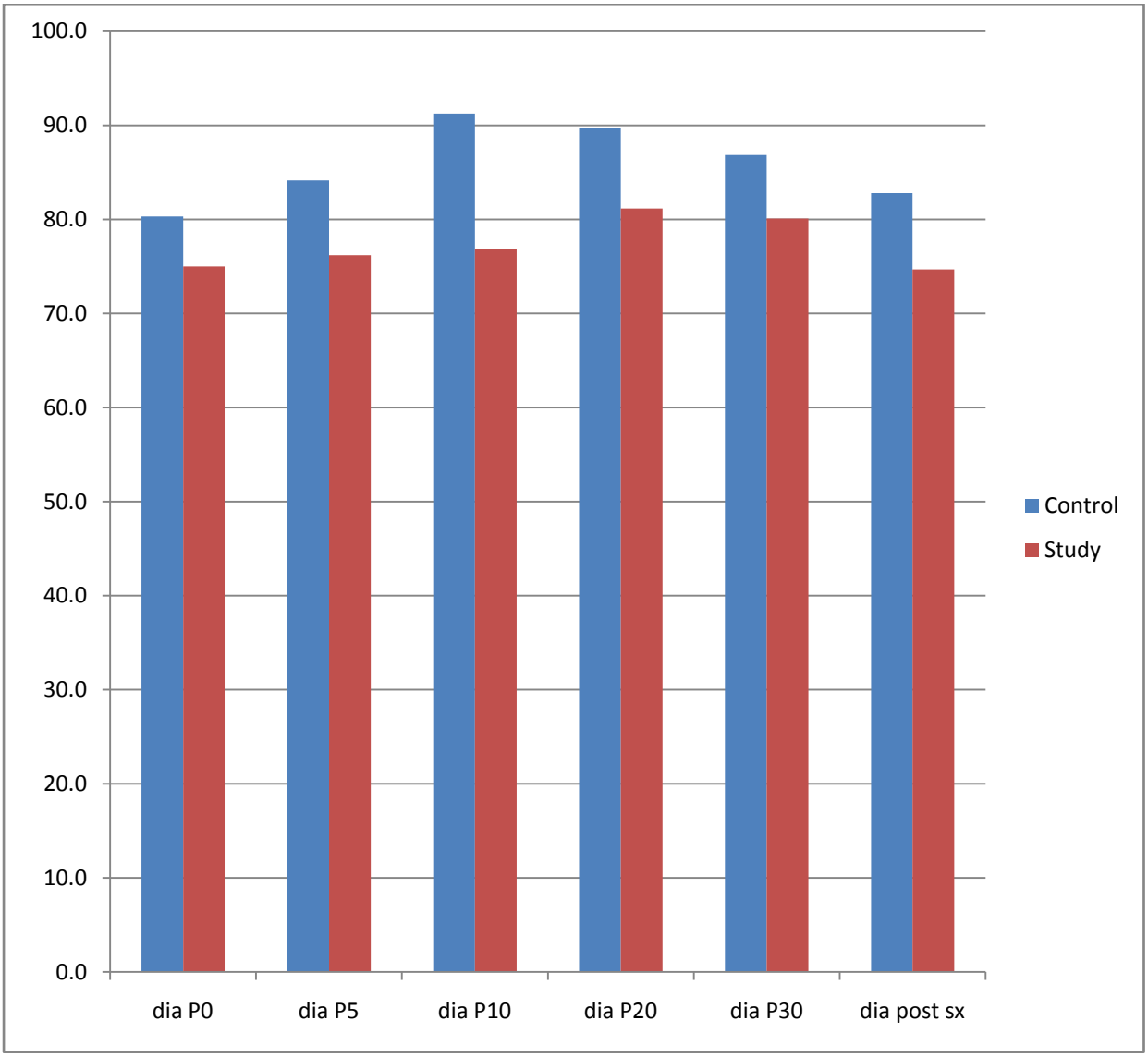


Chart-9 Bar diagram shows diastolic blood pressure is significantly lower (p value < 0.05) in study group than the control group at all point of time.

MEAN BLOOD PRESSURE

VARIABLE	CONTROL (GROUP A)	STUDY (GROUP B)	P VALUE
MEAN P 0	92.9	85.7	0.000
MEAN P5	98.5	87.5	0.000
MEAN P 10	104.9	89.3	0.000
MEAN P 20	102.8	94.3	0.000
MEAN P 30	99.0	94.5	0.003
MEAN POST SURGERY	94.7	84.7	0.001

P value <0.05 - significant

Test method – student t test

The mean blood pressure is significantly low in the study group (group B) than the control group (group A) during the period of pneumoperitoneum at 0 min (85 VS 92), 5th min (87 VS 98), 10th min(89 VS 104), 20th min (94 VS 102) and 30th min (94 VS 99) and also post surgery(84 VS 94). (chart-10)

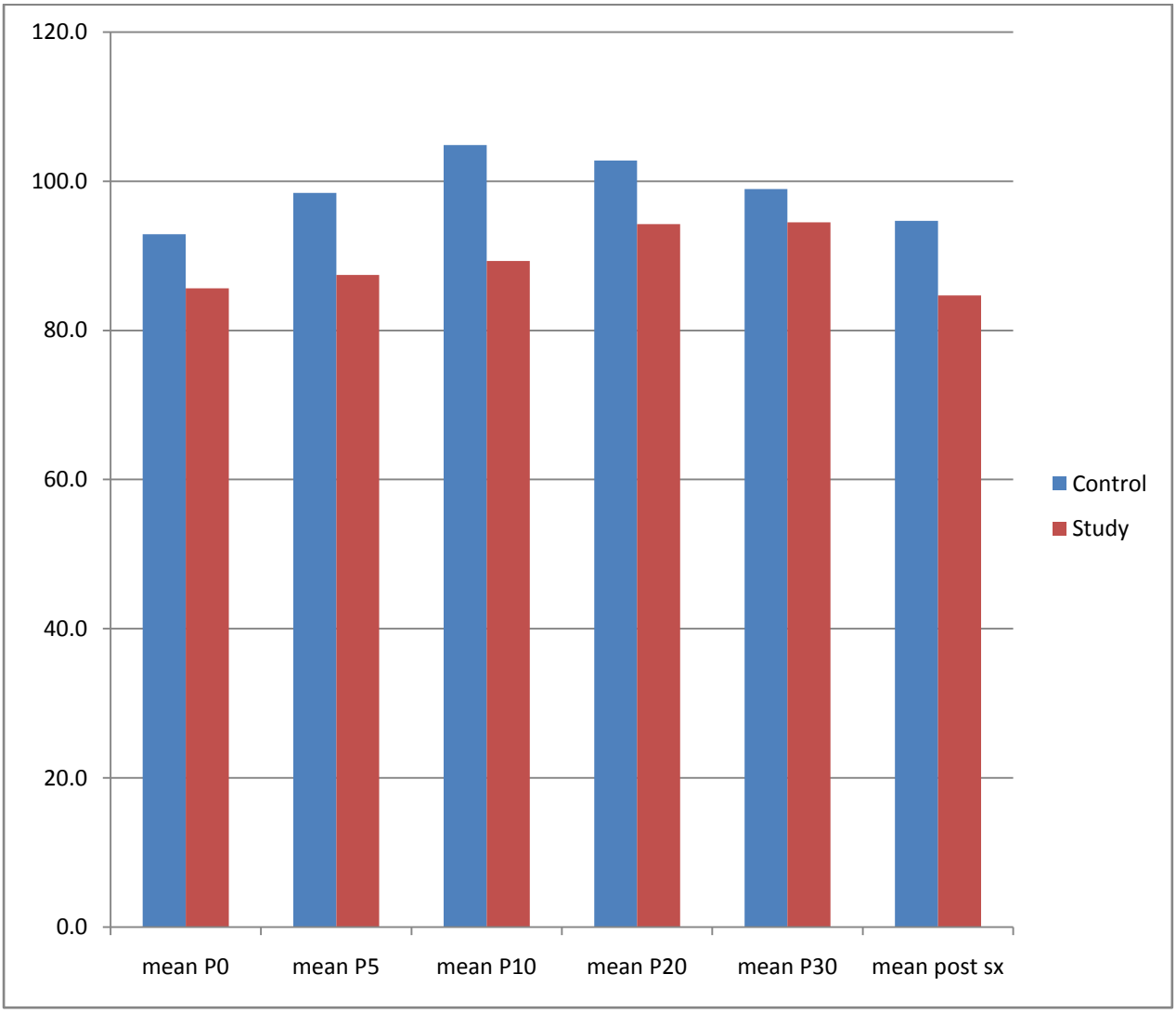


Chart-10 Bar diagram shows mean arterial pressure is significantly lower (p value < 0.05) in study group than the control group at all point of time.

SERUM NORADRENALINE VALUES

VARIABLE	CONTROL (GROUP A)	STUDY (GROUP B)	P VALUE
PRE PNEUMO PERITONEUM	200.5	194.8	0.367
10 MIN PNEUMO PERITONEUM	481.0	302.3	0.000

P value <0.05 significant

The nor adrenaline values are not significant between the control group (group A) and the study group (group B) before pneumoperitoneum (200.5 vs 194.8 pg/ml).

But the values between the control group (group A) and the study group (group B) taken at 10 minute pneumoperitoneum are very much significant (481.0 vs 302.3 pg/ml) suggesting attenuation of hemodynamic response arising due to CO_2 pneumoperitoneum. (chart -11)

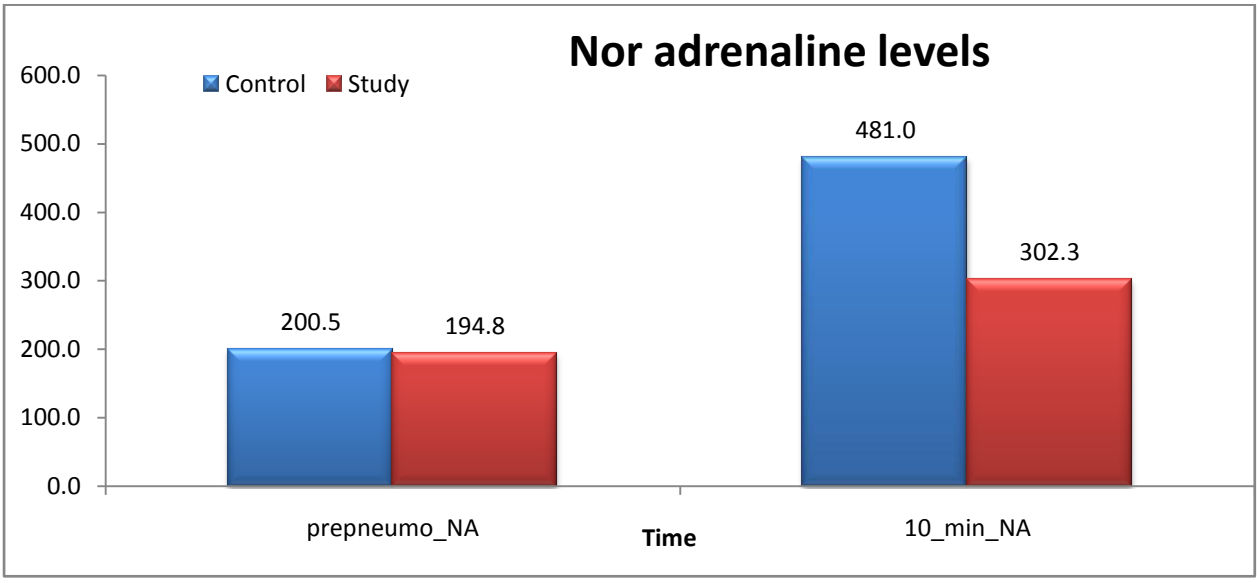


Chart-11 Bar diagram shows that noradrenaline levels are higher in the control group after induction of pneumoperitoneum but there is significant lower levels in the study group after induction of pneumoperitoneum.

DISCUSSION

In this study, neurohormonal hemodynamic response of dexmedetomidine in attenuating the arterial pressure increase is studied. The results obtained showed an effective attenuation of blood pressure and heart rate in patients who received dexmedetomidine as compared to the patients who received normal saline. The study also showed that dexmedetomidine effectively suppressed the noradrenaline release due to pneumoperitoneum in the patients who received dexmedetomidine but not in patients who received normal saline. Thus proving that dexmedetomidine acts by suppressing the central sympathetic outflow (sympatholytic) there by suppressing the hemodynamic changes induced by the CO_2 pneumoperitoneum.

Many studies have been done on laparoscopic surgery and highlighted hemodynamic changes during pneumoperitoneum and also proved by endocrine co relates the reason for the pneumoperitoneal response. The landmark study which was conducted about the hemodynamic response of laparoscopy with CO_2 pneumoperitoneum by Jean L. Loris et al which was published in JACC 1998,[26] showed that there is significant reduction of cardiac output and increase in mean arterial pressure and systemic vascular resistance. In the present study we also observed that systolic, diastolic and mean arterial pressure increased abruptly after induction of pneumoperitoneum and this response

sustained during the entire pneumoperitoneum period in the control group (group A) as observed by the previous studies.

Dexmedetomidine being a anxiolytic, sedative and sympatholytic effectively suppresses the stress response in various situations. In the study by Poonam S.Ghodki et al in journal of Anaesthesiology clinical pharmacology 2012,[20]studied dexmedetomidine as an anaesthetic adjuvant in laparoscopic surgery and they concluded dexmedetomidine is an effective adjunct without the fear of awareness under anaesthesia and resulted in 62.5% reduction in induction dose of propofol and 30% less end tidal isoflurane required. Similarly Clonidine which is congener of dexmedetomidine has been studied in attenuating the stress response in laparoscopic surgeries.

In the study by Jean L. Loris et al[26] that found that Clonidine effectively attenuated the stress response due to pneumoperitoneum. Similarly in our study we found that in the dexmedetomidine group (group B) hemodynamic responses to the induction of pneumoperitoneum were effectively blunted and the heart rate and blood pressure levels when compared to the control group (group A). Even though study conducted by D.Jee et al, published in British Journal of Anaesthesia 2009, [27] studied the effect of magnesium sulphate on pneumoperitoneum response showed that there is no change in heart rate in the magnesium group when compare to control group. But Jean L,Loris showed that Clonidine significantly reduced both heart rate and blood pressure.

Our study reports also show the same that dexmedetomidine attenuates both heart rate and blood pressure significantly.

ENDOCRINE CORRELATES OF LAPAROSCOPY

Loris et al[26] in his study showed the endocrine correlation of pneumoperitoneal response. The study showed that the reason the increase in the peripheral vascular response is due to increase in vasopressin and catecholamines levels. More precisely the study showed that vasopressin levels correlated closely with changes in peripheral vascular response. Induction of pneumoperitoneum causes rapid and marked release of vasopressin and it well co related with changes in intra abdominal pressure, intrathoracic and right atrial pressure. The reason for release of vasopressin is not clearly known and it may be probably due to mechanical stimulation of peritoneal receptors. Catecholamines particularly noradrenaline which was released during pneumoperitoneum also contributes to increase in peripheral vascular resistance. The stimulus for the release of noradrenaline is not known. The reason may be due to surgical stress induced by the pneumooeritoneum in laparoscopy.

Loris et al also studied the effect of Clonidine on laparoscopy and showed that Clonidine effectively attenuated the release of catecholamines and thereby decreasing the afterload. But study didn't showed correlation with vasopressin. Vasopressin and cortisol levels were same in both the groups. Since

dexmedetomidine has similar mode of action as Clonidine we assumed that vasopressin levels do not have much effect, so we selected to study nor adrenaline levels before and after pneumoperitoneum. In both study group and the control group, we studied the noradrenlaine levels before pneumoperitoneum and 10 minutes after induction of pneumoperitoneum.

In the control group (group A) the 10 minutes serum noradrenaline values were significantly higher than the pre pneumoperitneal values. This is similar to the studies conducted by Loris et al, [26] Lee et al, [27] Jens fromholt Larsen et al [29] on hemodynamic response of pneumoperitoneum.

In the study group (group B), where patients received 0.5μg/kg of dexmedetomidine as bolus dose over ten minutes before pneumoperitoneum, the noradrenaline levels taken 10 minutes after induction of pneumoperitoneum were significantly not increased when compared with the pre pneumoperitoneal values. Thus our study proved that the attenuation of arterial pressures by dexmedetomidine is due to suppression of catecholamines levels specifically noradrenaline by its central sympatholytic action. This is similar to studies conducted with dexmedetomidine by Pekka Talke et al[21] in attenuation of stress response by dexmedetomidine in vascular surgeries, and H.A.Mowafi et al [23] in attenuation of ocular pressure changes by dexmedetomidine.

Prolonged intraoperative increases of 20 mm of Hg or more in mean arterial pressure can cause significant implications in cardiovascular system. It

can cause increase incidence of myocardial ischemia, infarction and death. So by attenuating these responses in laparoscopy surgeries, dexmedetomidine may be of immense use in decreasing the morbidity in high risk cardiac patients. Our study concludes that dexmedetomidine can definitely be used for the attenuation of the hemodynamic responses arising due to CO_2 pneumoperitoneum.

SUMMARY

In our study,

- We observed, that the systolic, diastolic and mean arterial pressure increased abruptly after induction of pneumoperitoneum and this response sustained during the entire pneumoperitoneum period in the control group(group A).
- We observed that in the dexmedetomidine group(group B) hemodynamic responses to the induction of pneumoperitoneum were effectively blunted and the heart rate and blood pressure levels when compared to the control group(group A).
- In the control group (group A) the 10 minute serum noradrenaline values were significantly higher than the pre pneumoperitoneal values suggesting that all these hemodynamic changes are due to release of catecholamines.
- In the study group (group B), the noradrenaline levels taken 10 minutes after induction of pneumoperitoneum were significantly not increased when compared with the pre pneumoperitoneal values suggesting that dexmedetomidine effectively suppressed the hemodynamic responses by its central sympatholytic action.

CONCLUSION

We conclude that intravenous administration of dexmedetomidine as an adjunct before induction of CO_2 pneumoperitoneum in laparoscopic cholecyctectomy effectively attenuates the arterial pressure increase arising due to pneumoperitoneal response by suppressing the catecholamine release.

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PROFORMA

Name: I.P.No:

Age: Sex: Weight:

Pre Op Details:

Investigations:

Group: Study/ Control

Time Of Induction:

Time Of Start Of Surgery:

Time Of End Of Surgery:

Time Of Extubation:

Total Duration Of Anaesthesia:

Total Duration Of Surgery:

	Hr	Systolic	Diastolic	Mean	Etco2	IAP
Pre						
P 0						
P 5						
P 10						
P20						
P 30						
P 45						
Post						

Nor Adrenaline Values

Prepneumoperitoneum –

10 Minutes Pneumoreitoneum-

PATIENT CONSENT FORM

"To Determine The Effect Of Dexmedetomidine In Attenuating Arterial Pressure Increase During Laparoscopic Cholecystectomy"

Study Centre : Department of Anaesthesiology & Critical Care, Kilpauk Medical College.

Participant Name : Age : Sex :

O.P. No :

I ,confirm that I have understood the purpose of procedure for the above study. I had the opportunity to ask the question and all my questions and doubts have been answered to my satisifaction.

I have been explained about the pitfall in the procedure and the management of it. I have been explained about the safety, advantages and disadvantages of the techniques.

I understand that my participation in the study is voluntary and that I am free to withdraw at anytime without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to current study and any further research that may be conducted in relation to it, even if I withdraw from the study.

I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

I hereby consent to participate in this study of “To Determine The Effect Of Dexmedetomidine In Attenuating Arterial Pressure Increase During Laparoscopic Cholecystectomy”

Name of the patient : Signature / thumb impression of patient :

Name of the witness : Signature :

Address : Contact Number :

Name of the Investigator : Signature :

Time : Date :

Place :

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,CHENNAI-10

Ref.N.12054/MEI(Ethics)/2011 Dt: 03. 04.2012

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College , Chennai reviewed and discussed the application for approval entitled "A Study "To determine the effect of dexmedetomidine in attenuating arterial pressure increase during laparoscopic cholecystectomy" submitted by Dr. V.Santhosh, MD Anaesthesiology, Post Graduate, Govt.Kilpauk Medical College, Chennai-10 of this College.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE * Kilpauk, Chennai-10. * 04 MAY 2012

CHAIRMAN, 4/5/12
Ethical Committee
Govt.Kilpauk Medical College,Chennai

Dean
4/5/12 Kilpauk Medical College
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INTRODUCTION Surgical procedures and anaesthetic techniques and gadgets has improved over decades with recent advances and there is drastic fall in the mortality and morbidity. As a result of that there is consequent reduction in health care cost. With the invent of

2**better equipment and** modern **facilities, along with increased knowledge and**

better **understanding of anatomy,** physiology **and**

pathophysiology, has lead to the development of laparoscopy for diagnostic and operative procedures. The

2**pneumoperitoneum and the patient positions required for laparoscopy induce** a sequence of **pathophysiologic changes**

in terms of increased intra abdominal pressure(IAP) and systemic CO2 absorption that can complicate anaesthesia. Hence better understanding of the CO2 pneumoperitoneum in laparoscopy is important for the anesthesiologist for better management of the patient. Moreover with the advancements in medical field there is increase in the life expectancy. So as anaesthesiologist we are expected to anaesthetise elderly patients with associated co morbid conditions, like diabetes, hypertension, Ischemic heart disease etc. So understanding the physiology of CO2 pneumoperitoneum becomes very much essential. The multiple benefits like reduced hospital stay, post operative pain, respiratory complications and less cost

3**reported after laparoscopy** explains **its increasing use** and **has now become the standard technique for cholecystectomy. However, the** CO2 **pneumoperitoneum required for laparoscopy results in pathophysiologic changes particularly in cardiovascular**

system and respiratory system like 10-30 %

5**decrease in cardiac output,** significant **increase in** arterial pressure **and** systemic **vascular resistances**

occurring soon

3**after the beginning of** intra abdominal **insufflation, with no significant changes in heart rate (HR).**

3**Both mechanical and neurohumoral factors contribute to these hemodynamic changes.**

There is an increase in catecholamines, prostaglandins, rennin and vasopressin levels. There are lot of

anaesthetic methods and anaesthetic drugs has been used for attenuating the response associated with pneumoperitoneum. It has been already studied that Clonidine, alpha2-adrenergic agonists effectively attenuates the pneumoperitoneal response of the laparoscopy. Recently, dexmedetomidine is another drug of same family but more specific than Clonidine with better safety profile.

3**We therefore tested the hypothesis that** dexmedetomidine **might attenuate the hemodynamic changes induced by**

increased intra abdominal pressure due to CO2 pneumoperitoneum by reducing release of noradrenaline. PATHOPHYSIOLOGY OF CARBON DIOXIDE PNEUMOPERITONEUM HISTORY OF LAPAROSCOPY In the year 1901 , George Kelling first introduced CO2 pneumoperitoneum for laparoscopic surgeries. Till 1970s laparoscopy was done only for diagnostic purposes. Later in 1970 therapeutic procedure was started with laparoscopy in gynecology like laparoscopic sterilisation. 1n 1990s laparoscopy was used for cholecystectomy. With further technical advancement, laparoscopy is used for many abdominal surgeries. PHYSIOLOGIC EFFECTS: An important step in all laparoscopy is creation of pneumoperitoneum that is insufflation of gas into the peritoneal cavity for better visualisation of the abdominal contents. Pneumoperitoneum induce both mechanical and physiological changes in various system in the body especially in cardiovascular, respiratory and peripheral vascular system. The systems include 1. • Cardiovascular system 2. • Respiratory system 3. • Renal system 4. • Gastrointestinal system 5. • Peripheral vascular system CHANGES IN CARDIOVASCULAR SYSTEM Peritoneal insufflation to IAPs higher than 10 mm Hg induce significant alterations of hemodynamics of the patient. The changes in the cardiovascular system includes decrease in cardiac output, increased arterial pressures, and elevations of systemic and vascular resistances. Heart rates remain

5**unchanged or** increased **only slightly. The** changes **in cardiac output**

either increase or decrease is proportional to the increase in IAP. These changes might be caused by differences in rates of CO2 insufflation, IAP, degree of patient

2**tilt, time intervals between insufflation and collection of data, techniques** used **to assess hemodynamics,** and anesthetic techniques. **However,** most **studies** have shown **a** fall **of cardiac output** (10% **to** 30%) **during peritoneal insufflation whether the patient was placed in the head-down** (1) **or head-up position.**

(2) The mechanism for decrease in cardiac output is multifactorial. A decrease in venous return is observed after a transient increase in venous return at low IAPs (<10 mm Hg). Increased IAP results in IVC compression, thereby causing venous stasis in the legs, reduces the venous return and preload decreases. Transesophageal echocardiography showed reduction in LVEDV (left ventricular end-diastolic volume) during pneumoperitoneum thereby reasoning the decrease in cardiac output is due to decrease

5**in venous return.** (3) **Cardiac filling pressures,** however, rise **during**

peritoneal insufflations is due to increase in intra thoracic pressure accompanying to pneumoperitoneum. Hence

5**right atrial** pressure **and pulmonary artery occlusion** pressure **can no longer be considered reliable indices of cardiac filling** pressures **during pneumoperitoneum.**

The fact that atrial natriuretic peptide concentrations remain low despite increased pulmonary capillary occlusion pressure during pneumoperitoneum further suggests that abdominal insufflation interferes with venous return. (4) By increasing the circulating volume (preloading) before induction of pneumoperitoneum the decrease in venous return and cardiac output can be attenuated. Increased filling pressures can be achieved by fluid pre loading or slight head-down position of the patient before peritoneal insufflation, by preventing the pooling of blood with intermittent sequential pneumatic compression device or by wrapping the legs with elastic bandages. The ejection fraction of the left ventricle, assessed by echocardiography, does not appear to decrease significantly when IAP increases to 12 mm Hg. However, all studies describe an increased systemic vascular resistance during the existence of the pneumoperitoneum. This increase in afterload is not due to

3**reflex sympathetic response to decreased cardiac output.**

3**Although the normal heart tolerates increases in afterload under physiologic conditions, the** increases **in afterload produced by**

the presence of a pneumoperitoneum can be deleterious to cardiac patients. The increase in systemic vascular resistance is affected by patient position. The Trendelenburg position attenuates this increase; (1) the head-up position aggravates it. (2) The increase in systemic vascular resistance can be corrected by the administration of vasodilating anesthetic agents, such as isoflurane or sevoflurane, or direct acting vasodilating drugs, like nitroglycerin or nicardipine ,or centrally acting sympatholytic drugs like Clonidine.

5**The increase in systemic vascular resistance is** thought to be **mediated by mechanical** and **neurohumoral factors. The**

alterations in the hemodynamic parameters returns to normal baseline values after

3**several minutes suggesting involvement of** neurohormonal **factors.**

Catecholamines, the

2**renin-angiotensin system, and especially vasopressin are** all released during **the**

presence of the CO2 pneumoperitoneum and may contribute to increasing the afterload. (5) However, only the time course of vasopressin release parallels that of the increase in systemic vascular resistance. (5)

3**Increases in plasma vasopressin** concentrations correlate **with changes in** intrathoracic **pressure and transmural**

right atrial pressure.

3**Mechanical stimulation of peritoneal receptors also** results **in** increased **vasopressin release,**

systemic vascular resistance, and

3**arterial pressure.** (6) **However, whether increasing** IAP **to 14 mm Hg is sufficient to stimulate these** mechanical **receptors is**

not clear. The increase in systemic vascular resistance

2**also explains why the arterial pressure increases** but **the cardiac output falls.**

Use of α 2 -adrenergic agonists such as Clonidine (7) or dexmedetomidine and of β-blocking agents significantly reduces hemodynamic changes and anesthetic requirements. Use of high doses of remifentanil almost completely prevents the hemodynamic changes. CHANGES IN RESPIRATORY SYSTEM VENTILATORY CHANGES Pneumoperitoneum decreases thoracopulmonary compliance by 30% to 50% in healthy and obese patients. (8) Reduction in functional residual capacity and development of basal atelectasis due to elevation of diaphragm and changes in the distribution of pulmonary ventilation and perfusion from increased airway pressure can be expected. However, increasing IAP to 14 mm Hg with the patient in a 10- to 20-degree head-up or head-down position does not have significant effect on

physiological dead space or shunt fraction in patients without cardiovascular problems. INCREASE IN THE PARTIAL PRESSURE OF ARTERIAL CO2 During uneventful CO2 pneumoperitoneum, the partial pressure of arterial carbon dioxide (PaCO2) progressively increases to reach a plateau 15 to

> 730 minutes after the beginning of CO2 insufflation in patients under controlled mechanical ventilation during gynecologic laparoscopy in

the Trendelenburg position or during laparoscopic cholecystectomy in the head-up position. After that plateau period any increase in PaCO2 is

> 5independent of or related to CO2 insufflation

and search for other causes such as CO2 subcutaneous emphysema has to be thought. The

> 5increase in PaCO2 depends on the

IAP.

> 5During laparoscopy with local anesthesia, PaCO2 remains unchanged but minute ventilation significantly increases

due to CO 2 . Capnography and pulse oximetry provide reliable monitoring of PaCO 2 and arterial oxygen saturation in healthy patients and in the absence of acute intraoperative disturbances. The increase of PaCO 2 is multifactorial and the various reasons attributed are : ?

> 7absorption of CO 2 from the peritoneal cavity, ? mechanical compression of

the abdominal contents, patient position and controlled ventilation can cause impairment of pulmonary ventilation and perfusion. Studies have observed that there is increase in PaCO2 levels mainly when CO2 is used as inflating gas and not when nitrous oxide (N 2 O)

> 7or helium is used as inflating gas suggesting that the main mechanism of the increased PaCO2 during CO2 pneumoperitoneum is absorption of

CO2 and primarily due to mechanical ventilatory repercussions of increased IAP. (9) ↑ IAP ↑ CO2 ↑

cephalad shift of diaphragm Hypercapnia ↑ intra thoracic pressure ↓chestwall compliance Paradoxic diaphragm motion ↓ TV ↑ RR ↑ PAWP Alveolar collapse ↓ FRC ↑Ve & work of breathing Accordingly, direct measurement of CO2 elimination VCO2 using a metabolic monitor combined with investigation of gas exchange showed a 20% to 30% increase of VCO2 without significant changes in physiologic dead space in healthy patients undergoing pelvic laparoscopy (IAP of 12 to 14 mm Hg) in the head-down position or laparoscopic cholecystectomy in the head-up position. Mismatched ventilation and pulmonary perfusion can result from the position of the patient and from the increased airway pressures associated with abdominal distension. CHANGES IN PERIPHERAL VASCULAR SYSTEM Increased IAP and the head-up position result in stasis of blood in lower limbs. Blood flow through femoral vein decreases progressively with increasing IAP, and no adaptation to the reduced femoral venous outflow occurs, even during prolonged procedures thereby predisposing the patient to the development of thromboembolic complications. Although cases of thromboembolism have been reported in the literature, there is no actual increase in incidence during laparoscopy. ↑IAP ↓vascular resistance Reverse trendenlenberg Venous stasis ↑ risk of DVT CHANGES IN RENAL SYSTEM The effect of CO2 pneumoperitoneum on renal function has also been investigated. During laparoscopic cholecystectomy when compared to open cholecycstectomy there is less than 50% decrease in baseline values of renal plasma flow, glomerular filtration rate and urine output. Urine output significantly increases after deflation. ↑CO2 ↑IAP RAAS ↓ERPF ↓GFR ↓urine output CHANGES IN HEPATIC SYSTEM Controversy exists regarding the

5**effect of** the **CO2 pneumoperitoneum on splanchnic** and hepatic **blood flow.**

A significant reduction was reported in animal and humans. However, others have not observed any significant changes. Blobner and coworkers, (10) comparing CO2 pneumoperitoneum and air pneumoperitoneum in pigs, observed a reduction in splanchnic blood flow during air pneumoperitoneum but not during CO2 pneumoperitoneum. They suggest

5**that the direct splanchnic vasodilating effect of CO2** may counteract **the mechanical effect of increased**

IAP. ↑IAP ↓splanchanic blood

11**flow ↓portal** blood **flow ↓hepatic artery flow ↓perfusion** to bowel **↓hepatic perfusion ↓intestinal& gastric pH**

↑LFT CHANGES IN CENTRAL NERVOUS SYSTEM Cerebral blood flow increases during CO2 pneumoperitoneum in response to the increased PaCO2. (11) When normocarbia is maintained, pneumoperitoneum combined with the head-down position does not cause any change in intracranial dynamics. Intracranial pressure nevertheless rises during CO2 pneumoperitoneum, independently of changes in PaCO2, in pigs with preoperative induced intracranial hypertension or normal intracranial

pressure and in children with ventriculoperitoneal shunts. Intraocular pressure is not affected by pneumoperitoneum in women with no preexisting eye disease. In an animal model of glaucoma, pneumoperitoneum only slightly increases intraocular pressure. POSITION RELATED CHANGES Patient positioning depends on the surgical site; trendelenberg position

> 2**is used for pelvic and** lower abdominal **surgery,** reverse trendelenberg **position is** used **for** upper abdominal **surgery.**

These positions can cause changes in the hemodynamics that can have effect on the organ system. These positional changes will add up to the changes induced by laparoscopy thereby complicating the clinical scenario. So in laparoscopy, position of the patient definitely have an impact on the following patient hemodynamics.

> 2**CARDIOVASCULAR EFFECTS In** clinically normal **subjects, the head-down position**

or the trendelenberg causes increase in venous return and so preload increases and cardiac output increases. The increase in the cardiac output activates the baroreceptor reflex thus causing vasodilatation and bradycardia. However these changes caused by the position during laparoscopy does not have any significant change in hemodynamics in a normal healthy adult because in general anaesthesia these reflexes are blunted. (2) But these changes can lead to deleterious effects on patients who have poor cardiorespiratory reserve. The Trendelenburg position or the head low position causes passive venous congestion in the cerebral circulation and can cause in elevation of intraocular pressure and this may be deleterious in patients with angle closure glaucoma. But the advantage of this position is that it decreases the intravascular pressure in the lower part of the body like in pelvic organs and reducing the blood loss. But due to decreased intravascular pressure the chances of embolism is increased. With the head-up position or reverse trendelenberg position, there is a decrease in venous return and thereby cardiac output and the mean arterial pressure decreases. Since pneumoperitoneum induced by laparoscopy also causes decrease in cardiac output the, changes in position will add up these changes. So more the angulations of the head up more will be the fall in cardiac output. This may not have much effect on a normal adult but will have deleterious effects in cardiac patients. Lithotomy position may aggravate the hemodynamic changes by decreasing the venous return and this may be aggravated in head up position. Because pneumoperitoneum can further cause pooling of blood in the legs any other factor decreasing the venous return contributing to circulatory dysfunction should be avoided. Precautions such as supporting the legs, modified lithotomy, adequate padding on the popliteal space, pneumatic compression decompression device and avoiding tight strapping of legs should be taken. RESPIRATORY CHANGES The head-down position or tredenlenberg position can cause lung atelectasis of basal segments. Steep head-down position causes decrease in total lung volume, functional residual capacity and the pulmonary compliance. In healthy patients these changes does not have any major change in hemodynamics and have significant effect on elderly patient or obese patients. The

2**head-up position is considered to be more** favourable **to respiration.**

NERVE INJURY Head down position with shoulder brace can cause compression of brachial plexus and supraclavicular nerves and can lead to complications. Arms and elbows should be adequately padded and overextension of brachial plexus and ulnar nerve should be avoided. Lower extremity neuropathies and compartment syndromes

2**have been reported after laparoscopy. The common peroneal nerve is**

entrapment is more common in surgeries requiring lithotomy and can be prevented by padding the popliteal region. ADVANTAGES AND DISADVANTAGES OF LAPAROSCOPY The advantages include the ? Cosmetic results of small, non–muscle-splitting incisions and scars, ? Decreased blood loss, ? Less postoperative pain and ileus, ? Shorter hospitalization and convalescence, and ? Lower cost. ? Less post operative complications. Wound complications such as infection and dehiscene and incisional hernia are less frequent, and host defense mechanisms may be greater in laparoscopic than in open surgery. The disadvantages include the ? Laparoscopy is not suitable for patients with poor cardiac reserve and patients with severe respiratory disease, ? Long learning curve for the surgeon (most complications occur during the first 10 laparoscopies), ? The narrowed two-dimensional visual field on video, ? The need for general anesthesia, and the often longer duration. ? Ideally, surgeons should have more advanced laparoscopic skills, especially in knot tying, suturing, and working two instruments simultaneously. ? CO2 pneumoperitoneum induced hemodynamic complications.

5**ALTERNATIVES TO CO2 PNEUMOPERITONEUM** Newer techniques **have been** investigated **to reduce the**

hemodynamic changes induced by CO2 pneumoperitoneum in laparoscopy. These include ? Inert gases instead of carbon dioxide ? Gasless laparoscopy INERT GASES

7**Insufflation of inert** gas **like helium** or **argon** instead of CO2 **avoids the increase in**

PaCO2 and its consequences. (12) And hence

7**hyperventilation is not required,** but the **ventilatory** changes **of** the **increased IAP persist. The hemodynamic** changes produced by **pneumoperitoneum using inert** gas **are similar to**

CO2 pneumoperitoneum. Unfortunately, the

> 7low blood solubility of the inert gases may increase the risk of

gas embolism and this safety issue has to investigated. GASLESS LAPAROSCOPY Another alternative is

> 7gasless laparoscopy. The peritoneal cavity is expanded using abdominal wall lift obtained with a fan retractor. This technique avoids the hemodynamic and respiratory complications of increased IAP and also the consequences of the use of CO2.

Renal and splanchnic perfusion is not altered. Port-site metastases after laparoscopic surgery for cancer are reduced after gasless laparoscopy. This technique, therefore, is advantages for cardiac and pulmonary disease patients. However, gasless laparoscopy compromises surgical exposure and demands expertise. Combining abdominal wall lifting with low pressure CO2 pneumoperitoneum (5 mm Hg) may improve surgical conditions. PHARMACOLOGY OF DEXMEDETOMIDINE HISTORY The α

> 192 -adrenergic agonists provide sedation, anxiolysis, hypnosis, analgesia, and sympatholysis.

The initial use of α2 agonist in the anaesthesia are made by the observations of Clonidine. This was soon followed by a description of the minimum alveolar concentration (MAC) reduction of halothane by clonidine. Dexmedetomidine

> 1is a more selective α 2 agonist than Clonidine. It has α

2: α 1 specificity of 1600 : 1 when compared to Clonidine which has 200:1. It

> 1was introduced in clinical practice in the United States in 1999 and approved by the FDA only as a short-term (<24 hours) sedative for mechanically ventilated adult ICU patients. Dexmedetomidine is now being used

in operation theatres apart from ICU in various settings, including sedation and adjunct analgesia in the operating room, sedation in diagnostic and procedure units, and for other applications such as withdrawal/detoxification amelioration in adult and pediatric patients. PHYSICOCHEMICAL CHARACTERISTICS Dexmedetomidine is the d-enantiomer of medetomidine, a substance that has been

used for sedation and analgesia in veterinary medicine for many years. The chemical name is (S)-4-[1-(2,3-dimethylphenyl)ethyl]-3H-imidazole .

1**Dexmedetomidine belongs to the imidazole subclass of α 2 receptor agonists, similar to clonidine. It is freely soluble in water. METABOLISM AND PHARMACOKINETICS** Dexmedetomidine **has** a **rapid** distribution **half life**

and extensively metabolized in the liver and

1**excreted in urine and feces. The** major pathway **of** metabolism **is**

conjugation (41%) followed by methylation (21%).

1**Dexmedetomidine is 94% protein bound, and its concentration ratio between whole blood and plasma is 0.66.**

Dexmedetomidine has profound effects on cardiovascular variables and may alter its own pharmacokinetics. With large doses, there is marked vasoconstriction, which probably reduces the drug's volumes of distribution. In essence, dexmedetomidine displays nonlinear pharmacokinetics. The elimination half-life of dexmedetomidine is 2

16**to 3 hours,** with a **context-sensitive half-time** ranging **from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion.**

Postoperative patients sedated with dexmedetomidine display similar pharmacokinetics to the pharmacokinetics seen in volunteers. PHARMACOLOGY Dexmedetomidine is a nonselective α 2 agonist. Alpha 2 adrenoreceptors are membrane-spanning G proteins. Intracellular

26**pathways include inhibition of adenylate cyclase and modulation of ion channels.** There **are**

three subtypes of α 2 adrenoreceptors :

1**α 2A , α 2B , and α 2C** . In humans **the α 2A** receptors **are primarily distributed in the periphery,** and **α 2B and α 2C are** present **in the brain and spinal cord.**

Postsynaptic located α 2 adrenoreceptors in peripheral blood vessels produce vasoconstriction, whereas presynaptic α 2 adrenoreceptors inhibit the release of norepinephrine, potentially attenuating the vasoconstriction. The

1**overall response to α 2 adrenoreceptors agonists is related to the stimulation of α 2 adrenoreceptors located in the CNS and spinal cord.**

These receptors are involved in the sympatholysis, sedation, and antinociception effects of α 2 adrenoreceptors.

1**EFFECTS ON THE CENTRAL NERVOUS SYSTEM SEDATION The**

sedative effect of the α 2 agonists is due to the

1**action on α 2 receptors in the locus caeruleus and an analgesic**

effect is result of

1**action at α 2 receptors within the locus caeruleus and the spinal cord.**

(13) The quality of sedation produced by dexmedetomidine seems different compared with that produced by other sedatives acting through the GABA systems. Patients receiving dexmedetomidine infusions as part of their sedation regimen in the postoperative ICU setting have been described as being very easy to wake up and having the ability to follow commands and cooperate while being tracheally intubated. Undisturbed, patients were noted to fall asleep right away. Dexmedetomidine causes less respiratory depression inspite causing good sedation providing a wide range of safety margin. The sedative effect is due to action of

1**α 2 agonists through the endogenous sleep-promoting pathways.**

Dexmedetomidine produces a decrease in activity of the projections of the locus caeruleus to the ventrolateral preoptic nucleus. This increases GABAergic and galanin release in the tuberomammillary nucleus, producing a decrease in histamine release in cortical and subcortical projections. The α 2 agonists seem to inhibit ion conductance through L-type or P-type calcium channels and facilitate conductance through voltage-gated calcium-activated potassium channels. The similarity between natural sleep (non–rapid eye movement) and dexmedetomidine-induced hypnosis has been speculated to

maintain cognitive and immunologic function in the sleep-deprived states (as in the ICU). The α 2 agonists

19**have the advantage that their effects are readily reversible by**α 2 **- adrenergic antagonists**

(e.g., atipamezole). Atipamezole is not currently approved for human use. Similar to other adrenergic receptors, the α 2 agonists also show tolerance after prolonged administration. Dexmedetomidine can be employed for addiction treatment; dexmedetomidine has been described for use in rapid opioid detoxification, cocaine withdrawal, and iatrogenic induced benzodiazepine and opioid tolerance after prolonged sedation.

1**ANALGESIA The analgesic effects of dexmedetomidine are complex.** Dexmedetomidine **do have an analgesic effect when injected via** spinal **or epidural** . Clonidine injected in **the**

neural axis helps with short-term pain, cancer pain, and neuropathic pain. The effects on blood pressure are slower in onset with an epidural injection than with an intrathecal administration. Epidural effects are seen in 5 to 20 minutes.

1**The primary site of analgesic action is thought to be the spinal cord. Systemic use of dexmedetomidine shows narcotic sparing.**

There is 50% decrease in the narcotic requirement in ICU patients receiving dexmedetomidine for sedation in the post operative period. EFFECTS ON THE RESPIRATORY SYSTEM Dexmedetomidine in sedative doses causes reduction of minute ventilation but the ventilator response to hypercarbia is well maintained.

1**The changes in ventilation appeared similar to those observed during natural sleep.**

Ebert and colleagues, (14) infusing dexmedetomidine to concentrations of 15 ng/mL in spontaneously breathing volunteers, showed no change in arterial oxygenation or pH. At the highest concentrations, PaCO 2 increased by 20%. Respiratory rate increased with increasing concentration from 14 breaths/min to 25 breaths/min. When dexmedetomidine and propofol were titrated to equal sedative end points (BIS of 85), both resulted in no change in respiratory rate. In a study comparing the effects of remifentanil and dexmedetomidine on respiratory parameters in normal volunteers, the hypercapnic ventilatory response was unaffected even at doses that produced unresponsiveness to vigorous stimulation. PaCO 2 increased mildly with dexmedetomidine, but it reached a plateau after the first increment. Dexmedetomidine also

exhibited a hypercarbic arousal phenomenon, which has been described during normal sleep and is a safety feature.

> 1**EFFECTS ON THE CARDIOVASCULAR SYSTEM The** primary **effects of α 2 agonists on the cardiovascular system are** reduction in **heart rate, systemic vascular resistance; and**

thereby indirect reduction of

> 1**myocardial contractility, cardiac output, and systemic blood pressure.**

By developing highly selective α agonists, it has been hoped to decrease some of these adverse cardiovascular effects and to maximize the desirable hypnotic-analgesic properties. The

> 1**hemodynamic effects of a bolus** dose **of dexmedetomidine have shown a biphasic response.** After **an**

bolus IV injection of 2 µg/kg of dexmedetomidine, results in

> 1**an initial increase in blood pressure (22%) and decrease in heart rate (27%) from baseline that occurred at** within **minutes after**

induction. The reason for this initial increase of blood pressure is

> 1**due to the** direct **vasoconstrictive** effect **of dexmedetomidine** on **peripheral α 2 receptors. Heart rate** returned **to baseline by 15 minutes, and blood pressure**

gradually declined to approximately 15% below baseline by 1 hour. After an IM injection of the same dose, the initial increase in blood pressure was not seen, and heart rate and blood pressure remained within 10% of baseline. Ebert and colleagues (14) performed an elegant study in volunteers using a target-controlled infusion system to provide increasing concentrations (0.7 to 15 ng/mL) of dexmedetomidine . The lowest two concentrations produced a decrease in MAP (13%) followed by progressive increase (12%). Increasing concentrations of dexmedetomidine also produce progressive decreases in heart rate (maximum 29%) and cardiac output (35%). Infusion of dexmedetomidine in volunteers also has been shown to result in a compensated reduction in

15**systemic sympathetic tone without changes in baroreflex sensitivity.**

There is blunted response of

15**heart rate and systemic sympathetic activation** owing **to** sweating, **but is less effective in blunting cardiac sympathetic** response **to shivering.**

The

1**incidence of hypotension and bradycardia may be** due **to** loading dose of **the** drug. This incidence **of**

hypotension and bradycardia can be omitted or reduced by avoiding the bolus

1**dose or not giving more than 0.** 5 **µg/kg.**

1**Giving the loading dose over 20 minutes also** decreases **the** incidence of **transient hypertension.**

In several studies after IM and IV administration, dexmedetomidine caused, in a small percentage of patients, profound bradycardia (<40 beats/min) and occasionally sinus arrest/pause. Generally, these episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergics. It would be expected from its profile that dexmedetomidine would be beneficial to the ischemic myocardium. In animal models, dexmedetomidine showed some beneficial effects on the ischemic heart through decreased oxygen consumption and redistribution of coronary flow from nonischemic zones to ischemic zones after acute brief occlusion. Dexmedetomidine also decreases serum lactate in a dog model of coronary ischemia with an associated decrease in heart rate and measured catecholamines. It also produced an increase in the

27**endocardial/epicardial blood flow ratio by**

35%. The perioperative use of dexmedetomidine

27**reduces the incidence of** perioperative **myocardial ischemia.**

More recently, Wallace and associates (15) showed that the administration of clonidine in the preoperative period reduces the incidence of perioperative cardiac ischemia from 31% to 14%, and reduces the mortality for 2 years from 29% to 15% compared with placebo. The only data on potential benefits in perioperative ischemia prevention with dexmedetomidine are provided in an underpowered study in vascular surgery patients who received the drug in the perioperative period. Blood pressure and heart rate were lower in the dexmedetomidine group, but these patients also needed the use of more drugs intraoperatively to sustain blood pressure and heart rate. No reductions of ischemic events were noted. No rebound effects have been found when discontinuing dexmedetomidine drips, even when it is given for more than 24 hours. A frequently reported side effect of dexmedetomidine has been a dry mouth. Dry mouth is due to a decrease in saliva production. USES Dexmedetomidine has been approved for ICU sedation in patients needing ventilation less than 24 hours. The

1**well documented effects of anxiolysis, sedation, analgesia, and sympatholysis with minimal respiratory depression,** makes **it**

an ideal drug and

1**it also has been used in various other clinical scenarios. INTENSIVE CARE UNIT Dexmedetomidine has advantages** over propofol **for sedation** of **postoperative patients**

receiving mechanical ventilation. When both drugs were titrated to equal sedation as assessed by the BIS (approximately 50) and Ramsay sedation score (5), dexmedetomidine patients required significantly less narcotics (alfentanil 2.5 mg/hr versus 0.8 mg/hr). Heart rate was slower in the dexmedetomidine group, whereas MAP was similar. In the dexmedetomidine group the

1**PaO 2 /FIO 2 ratio was significantly higher.**

Time to extubation after discontinuation of the infusion was similar at 28 minutes. Patients receiving dexmedetomidine seemed to have greater recall of their stay in the ICU, but all described this as pleasant overall. The

1**decreased requirement for opioids (>50%) when dexmedetomidine is used for sedation compared with propofol or benzodiazepines**

has been confirmed by many studies. Most studies also describe more stable hemodynamics during weaning when dexmedetomidine is used for sedation. This is of obvious benefit in patients with high risk for

myocardial ischemia. For sedation in the ICU, loading

18**doses of 0.** 5 **to** 1 **µg/kg**

have been used. Infusion rates

18**of 0.1 to** 1 **µg/kg/**

hr are generally needed to maintain adequate sedation. Delirium in the ICU is a risk factor for increased length of stay and increased mortality. In a trial of sedation in ventilated patients with dexmedetomidine versus lorazepam, it was found that using dexmedetomidine infusions provided more days alive without delirium or coma and a greater amount of time spent at the appropriate sedation level compared with lorazepam. Clonidine

1**have been used in the treatment of alcohol and drug withdrawal.**

In a comparison between clonidine and chlordiazepoxide in the treatment of patients with alcohol withdrawal, clonidine proved to give better anxiolysis with better hemodynamics. Dexmedetomidine has been successfully used in the treatment of drug withdrawal. Maccioli (16) reported the successful use of dexmedetomidine in two adult patients, one with cocaine and alcohol withdrawal symptoms, and another with withdrawal from prolonged use of benzodiazepines and narcotics in the ICU. Dexmedetomidine controlled withdrawal behavior and allowed for successful detoxification of young cardiothoracic patients (spanning the ages of days to 17 years) who developed drug withdrawal from prolonged use of benzodiazepines and narcotics in the ICU. Hence dexmedetomidine has been useful in narcotic, alcohol and benzodiazepine withdrawal. The unique characteristics of dexmedetomidine

1**—providing adequate sedation with minimal respiratory depression—can be used when weaning patients from the ventilator.**

Siobal and colleagues (17) reported the successful weaning of five ventilated patients who had failed weaning secondary to agitation. Infusions of dexmedetomidine of 0.5 to 0.7 µg/kg/hr were used (no loading) and permitted the discontinuation of propofol in four of five patients. All patients were extubated while still on the dexmedetomidine infusion. One patient required reintubation for upper airway obstruction. The use of dexmedetomidine to facilitate daily “wake up” tests in mechanically ventilated patients seems attractive, but few data have been published. The FDA approved the use of dexmedetomidine infusions for 24 hours or less. Multiple studies have shown the safety of using this drug for longer periods, however. In data collected from prescribing patterns in 10 institutions, it was shown that dexmedetomidine was used longer than 24 hours in 33.8% of cases. It also was noted that 33% of patients received a loading dose,

27% of patients received a dose higher than the recommended maximum, and 60% of patients remained on the infusion after extubation. ANESTHESIA As a premedicant, dexmedetomidine, at IV doses of 0.5 µg/kg given 15 minutes before surgery, seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia. Within this dosage range, dexmedetomidine reduces thiopental requirements (by ±30%) for short procedures, (18) reduces the requirements of volatile anesthetics (by ±25%), and more effectively attenuates the hemodynamic response to endotracheal intubation compared with 2 µg/kg of fentanyl. Dexmedetomidine also has been evaluated as an IM injection (2.5 µg/kg) with or without fentanyl administered 45 to 90 minutes before surgery. This regimen was compared with IM midazolam plus fentanyl and was found to provide equal anxiolysis, reduced response to intubation, smaller volatile anesthetic requirements, and a decreased incidence of postoperative shivering but a higher incidence of bradycardia. Atipamezole, a selective α 2 antagonist, at 50 µg/kg was effective in reversing the sedation of dexmedetomidine (2 µg/kg intramuscularly), when used to provide sedation for brief operative procedures. This reversal of effects resulted in a more rapid recovery than occurred after equisedative doses of midazolam.

1 **Dexmedetomidine has been used for sedation for monitored anesthesia care. In**

a study comparing the efficacy of dexmedetomidine or propofol as a sedative agent in a group of 40 patients receiving local anesthesia or regional blocks, dexmedetomidine (1 µg/kg given over 10 minutes) when used for intraoperative sedation resulted in a slower onset than propofol (75 µg/kg/min for 10 minutes), but similar cardiorespiratory effects when titrated to equal sedation. The average infusion rate of dexmedetomidine intraoperatively to maintain a BIS value of 70 to 80 was 0.7 µg/kg/min. Sedation was more prolonged after termination of the infusion, as was recovery of blood pressure. Smaller doses of opioid were needed in the first hour, however. Dexmedetomidine sedation has been done successfully in pediatric patients. Two studies, comprising 140 children 1 to 7 years old, reported successful sedation for MRI scans compared with midazolam or propofol. When

1 **dexmedetomidine is used as a premedication before general surgery for cataract removal, intraocular pressure is decreased (33%),** stress hormone **secretion is reduced, perioperative** narcotic **requirements are less, and recovery is more rapid. For**

maintenance of anesthesia, dexmedetomidine has been used in patients undergoing multiple types of surgery. In patients given an infusion regimen to achieve a plasma concentration of slightly less than 1 ng/mL, combined with 70% nitrous oxide, dexmedetomidine reduced isoflurane requirements by 90% compared with a control group. One retrospective study and two prospective, randomized controlled trials in bariatric surgical patients have found that a balanced anesthetic with desflurane or propofol plus dexmedetomidine (0.5 to 0.8 µg/kg bolus plus 0.4 µg/kg/hr infusion) reduces postoperative pain scores and morphine consumption, and improves hemodynamics compared with desflurane-fentanyl or propofol-

fentanyl anesthetics. In patients presenting for vascular surgery, three infusion rates of dexmedetomidine were compared with a placebo infusion starting 1 hour before surgery and administered until 48 hours after surgery. In the groups receiving dexmedetomidine, more vasoactive agents were required to maintain hemodynamics intraoperatively, but less tachycardia was noted postoperatively. No other

22**significant differences were noted between the groups.** Grant **and**

colleagues (19) described the use of dexmedetomidine when securing the airway with a fiberoptic intubation in three patients undergoing cervical spine surgery. The procedure was well tolerated with no hemodynamic compromise or respiratory depression. Because this drug provides good sedation with maintainence of respiration, it has been used in patients undergoing awake craniotomies with functional testing and electrocorticography or awake carotid endarterectomies with fewer fluctuations from the desired sedation level and more stable hemodynamics. Another use of dexmedetomidine has been as an anesthetic adjunct or sedative agent for patients who are susceptible to narcotic-induced respiratory depression or sleep apnea. This is evident in the use of dexmedetomidine in bariatric surgery. The addition of dexmedetomidine infusions to assist on transesophageal echocardiography examination has been described, with better hemodynamic profile and improved patient satisfaction than with benzodiazepine and narcotics alone, with no added respiratory depression. The use of dexmedetomidine has dramatically increased. This highly selective α 2 agonist has a set of unique effects that include titratable sedation, sympatholysis, and analgesia without significant respiratory depression. Originally approved as a sedative in the ICU, it has found many off-label applications in the ICU, the operating room, and perioperative environment. The off-label

23**use of dexmedetomidine in infants and children**

is rapidly increasing. More than 800

23**reports have been published regarding** its **use in**

this population. VARIOUS ANAESTHETIC TECHNIQUES FOR LAPAROSCOPIC SURGERY PREOPERATIVE EVALUATION OF THE PATIENT Without regard to surgical contraindications, absolute contraindications to laparoscopy and pneumoperitoneum are rare, and some still require characterization. Pneumoperitoneum is contraindicated in patients with increased intracranial pressure (e.g., tumor, hydrocephalus, head trauma) and hypovolemia. Laparoscopy can be performed safely in patients with ventricular peritoneal shunt and peritoneojugular shunt that are provided with unidirectional valve resistant to IAPs used during pneumoperitoneum. Cardiac patients coming for laparoscopic surgery,

2**cardiac function should be evaluated** because of **the hemodynamic changes** caused **by pneumoperitoneum and patient position**

can aggravate the present medical situation, particularly in a compromised ventricular function .

6**Patients with** severe **congestive heart failure and**

advanced valvular conditions are at increased risk

2**to develop cardiac complications** during laparoscopy **than patients with ischemic cardiac disease.** The choice of **laparoscopy**

verses laparotomy in these patients must be made taking in account, the

2**postoperative benefits of laparoscopy against the intraoperative risks of laparoscopy.**

Gasless laparoscopy may represent an alternative for these patients. Because of the side effects of increased IAP on renal function, patients with renal failure deserve special care to optimize hemodynamics during pneumoperitoneum, and the concomitant use of nephrotoxic drugs should be avoided. In

2**patients with respiratory disease,** even though **laparoscopy appears** superior **to laparotomy because of reduced postoperative respiratory dysfunction**

but in laparoscopy there is increased risk of pneumoperitoneum and risk of ventilation perfusion mismatching. DVT prophylaxis is the same for laparoscopy and laparotomy. PREMEDICATION

2**Premedication should be adapted** based on **the duration of the laparoscopy and to the necessity** for **quick recovery**

in daycare setting. All patients undergoing laparoscopy should receive antacid prophylaxis and an anti emetic preoperatively.

2**Preoperative administration of** IV paracetemol **may be helpful in reducing postoperative pain and opiate requirements.**

2**PATIENT POSITIONING AND MONITORING Patients must be positioned with great care to prevent nerve injuries; padding should protect from nerve compression**

at pressure points. The head up or head low position should be done slowly and gradually as sudden change in position may cause drastic changes in cardiovascular and respiratory system. The patient tilt should be restricted to 15 to 20 degrees. After intubation and postioning the patient, the position of endotracheal tube as to be checked since change in position may cause the tube to move in or move out resulting in accidental endobronchial or extubation respectively.

2**Induction and release of the pneumoperitoneum** should **be smooth and progressive. Mask ventilation**

should be as gentle as possible without inflating the stomach, if inflated also ryles tube should be placed and stomach decompressed before trocar placement to avoid gastric perforation specifically in upper abdominal laparoscopy procedures. Emptying of the bladder before all laparoscopic surgeries is must. RECOMMENDED MANDATORY MONITORING ‣ Electrocardiography ‣ Non invasive blood pressure ‣ Pulse oximetry ‣ Capnometry ‣ Temperature ‣ Invasive monitors like intra arterial blood pressure, central venous pressure,

2**transesophageal echocardiography** will **be more helpful in** case of **patients with severe cardiac disease.**

ANESTHETIC TECHNIQUES 1. General anaesthesia, 2. Local anaesthesia, and 3. Regional anesthesia All the three have all

2**been used successfully and safely for laparoscopy.** 1. **General Anesthesia General anesthesia with endotracheal intubation and controlled ventilation**

is certainly the safest and most commonly used

5**technique and** therefore **is recommended in** all **patients and for long laparoscopic procedures.**

? Choice of induction drugs does not have any role. Either of the induction drugs can be used, propofol, thiopentone or ethiomdate can be used. Profolol induction seems to be associated with lower incidence of

post operative complications. ? Although N2O is not contraindicated in laparoscopic procedures omission of its use seems to cause decreased bowel distention and improve the

9**surgical conditions for intestinal and colonic surgery.**

? Adequate analgesia with fentanyl or remifentanyl is required. ?

9**During pneumoperitoneum,** minute **ventilation must be adjusted to maintain**

PETCO 2 between 30 and 35 mm Hg by adjusting the respiratory rate rather than tidal volume and this may helpful in COPD patients by preventing barotraumas. ? IAP should be monitored, and kept ideally between 12-15 mm of Hg to reduce hemodynamic and respiratory changes. ? Adequate fluid management minimizes hemodynamic alterations. ? Muscle relaxation should be adequate especially during trocar placement. ? Infusion of vasodilating drugs, such as nitroglycerine, α 2 -adrenergic receptor agonists such as Clonidine, and remifentanil

9**reduces the hemodynamic** alterations **of pneumoperitoneum and** may **facilitate management of cardiac patients.** ? Choice **of**

inhalational agents – newer inhalational agents like sevoflurane, isoflurane or desflurane can be safely used. ? All patients should be reversed after adequate breathing attempts with neostigmine and glycopyrrolate and after adequate recovery patient should be shifted with PACU. The laryngeal mask airway may be an instead of endotracheal intubation even though it does not rule out the risk of gastric aspiration.

2**It allows controlled ventilation and accurate monitoring of**

PETCO 2 . Since pneumoperitoneum decreases the pulmonary compliance it

5**frequently results in** higher **airway pressures exceeding 20 cm**

H 2 O only ProSeal laryngeal mask airway which seal upto 30 cm of H 2 O can be used in laparoscopy. Short procedures using low intra abdominal pressure can be done with

2**general anesthesia in patients breathing spontaneously without intubation.**

It has an advantages over endotracheal intubation that avoids tracheal irritation and use of muscle relaxant. But it is not ideally recommended and its better to use an laryngeal mask airway in these type of patient for short procedures. Local and Regional Anesthesia It is ideally used for short procedures at day care set up.The advantages of of local anaesthesia over general anaesthesia include fast and better recovery, decreased post operative

> 2**nausea and vomiting, early** diagnosis **of complications, and** fewer **hemodynamic changes.**

Laparoscopic surgeries done under local anaesthesia needs

> 9**precise and gentle surgical technique and**

since it is always associated with

> 2**increased patient anxiety, pain, and discomfort during the** surgical **manipulation of organs, local anesthesia is** always **supplemented with intravenous sedation.**

> 9**Regional anesthesia,** both **epidural and spinal techniques, combined with the** trendelenberg **position can be used for gynecologic laparoscopy without major** hemodynamic or ventilatory **impairment.**

Laparoscopic cholecystectomy has been successfully performed using epidural anesthesia in COPD patients. The anaesthetic stress of general anaesthesia

> 2**is reduced by regional anesthesia.** Both **epidural and local anesthesia** have **the same benefits and disadvantages.** The advantages of **regional**

anaesthesia include decreased requirement of sedatives, better muscle relaxation than general anaesthesia. The disadvantages being it does not alleviate the discomfort due to abdominal distension and shoulder tip pain due diaphragmatic irritation, and chances that the level of block may rise due to increased intra abdominal pressure.

> 9**Extensive sensory block (T4-L5) is** usually **necessary for surgical laparoscopy**

and may also lead to discomfort. The epidural administration of opiates or clonidine, or dexmedetomidine, may **help to provide adequate analgesia**

and decreased hemodynamic response to CO2 pneumoperitoneum. In case of gaseless laparoscopy reginal anaesthesia can provide adequate analgesia.

2**POSTOPERATIVE MONITORING Hemodynamic monitoring should be** continued **in the**

PACU. The increased systemic vascular resistance, usually last for longer duration even after the release of pneumoperitoneum. After the release of pneumoperitoneum there exists a hyper dynamic circulation due to stagnating blood entering into the central circulation from peripheries, this could lead to adverse events in patients with cardiac disease. Even though there is decreased pulmonary complications in laparoscopy than laparotomy, PaO 2

2**still decreases after laparoscopic cholecystectomy.** There is **an increased** oxygen **demand in**

all post laparoscopy patients so it is always recommended to give supplemental oxygen, even to healthy patients. All patients should be given anti emetic to prevent post operative nausea and vomiting and should be provided adequate analgesia. PRACTICE GUIDELINES European Association of Endoscopic Surgery has given guidelines on Pneumoperitoneum for Laproscpic Surgery. They have given the monitoring guidelines for normal patients and high risk patients undergoing laparoscopic surgeries. ASA I/II patients Pneumoperitoneum of intra abdominal pressure of 12 – 15 mm of Hg rarely causes adverse hemodynamic effects (grade A). All the basic monitoring are recommended including end tidal CO2 (grade A). ASA III/IV It is advised in all high risk patients to go for alternative of gaseless laparoscopy (grade B) Even if pneumoperitoneum is indicated

2**IAP should be as low as possible to reduce** perfusion **changes** in renal, hepatic **and**

other organs (grade B). In all high risk cases thromboprophylaxis mandatory (grade A).

24**Sequential intermittent pneumatic compression of lower** extremities **is recommended for all prolonged laparoscopic procedures**

(grade A/B). In cardiac patients, ? Invasive monitoring is always indicated. Invasive blood pressure and

central venous pressure monitoring

11**(grade A) ? Adequate pre-op volume loading +/- B-blockers** is **recommended (grade A)**

In patients with poor respiratory reserve, ? Laparoscopic surgery definitely has better outcome than open method (gradeA) ?

11**Intra- and post-op ABG monitoring recommended (grade A)**

? Maintaining minute ventilation reduce respiratory acidosis (grade A) Grade A – strongly recommended and studies have proved it Grade B – it is advisable and definitely have positive outcome on the patients. REVIEW OF LITERATURE STUDIES RELATED TO CO2 PNEUMOPERITONEAL RESPONSE IN LAPRAROSCOPY 1. Jean L.Moris et al published in American College of cardiology, 1998, the

3**hemodynamic changes induced by** lapraroscopy **and** its **endocrine correlates** and **effects of Clonidine** on pneumoperitoneum. The **study** conclusion **was**

3**vasopressin and catecholamines probably** mediated **the increase in systemic vascular resistance observed during** pueumoperitoneum. **Clonidine** given **before** pneumoperitoneum **reduces** the **catecholamine release and attenuates hemodynamic changes during laparoscopy.**

(26) 2. D.Jee et al, published in British Journal of Anaesthesia 2009, the effect of intravenous

4**magnesium sulphate attenuates arterial pressure increase during**

laproscopic cholcystectomy. They concluded that intravenous magnesium sulphate 50 mg/kg given before pneumoperitoneum attenuated the arterial pressure increase due to pneumperitoneum.

4**This attenuation apparently related to** reduction **in release of** catecholamines and **vasopressin or both.**

(27) 3. K. Myre et al in Acta Anaesthesiologica Scandinavia, march 2003 have studied the effect of high

dose remifentanyl(0.39 µg/kg/min) infusion in attenuating the stress response to pneumoperitoneum in 18 patients undergoing laproscopic fundoplication . The study showed that high dose remifentanyl depressed epinephrine release to pneumoperitoneum. (28) 4. Jens fromholt Larsen et al, in Journal of Gasteroenterolgy surgery 2002, studied the effect of stress response of gasless and carbondioxide pneumoperitoneum. The study showed carbondioxide pneumoperitoneum induced significant change in stress hormones. (29) 5. Gopta.k et al in Saudi Journal of Amaesthesiology 2011, have studied the effect of oral pregabalin (150mg) and oral Clonidine (200µg) for hemodynamic stability during laryngoscpy and laproscopic cholecystectomy and said that both drugs causes anxiolysis and sedation with hemodynamic stability. (30) 6. Tripathi DC et al, in Journal of Anaesthesiology clinical pharmacology October 2011, have studied two different doses of intravenous Clonidine (1µg/kg and 2µg/kg) in attenuating hemodynamic stress response during laparoscopic cholecystectomy. The study concluded that Clonidine 2µg/kg intravenously given 30 minutes before induction is safe and effective preventing hemodynamic stress response during laparoscopy. (31 7. Maharajan SK in Kattmandu University Medical Journal 2005, studied the effect of propanalol in decreasing stress response in laparoscopic cholecystectomy and concluded that propanolol (1 mg intravenous) effectively blunts the stress response to carbondioxide pneumoperitoneum during laproscopic cholecystectomy. (32) STUDIES RELATED TO DEXMEDETOMIDINE FOR STRESS ATTENUATION 1. Poonam S.Ghodki et al in journal of Anaesthesiology clinical pharmacology 2012, studied dexmedetomidine as an anaesthetic adjuvant in laproscopic surgery and they concluded dexmedetomidine ia an effective adjunct without the fear of awareness under anaesthesia and resulted in 62.5% reduction in induction dose of propofol and 30% less end tidal isoflurane required. (20) 2. Pekka Talke et al, Department of Anaesthesia, University of California published a paper in Anaesthesia and Analgesia on

14**hemodynamic and adrenergic effects of perioperative** effects of **dexmedetomidine after vascular surgery.**

The study showed the group of patients receiving dexmedetomidine infusion had decrease heart rate and plasma nor adrenaline values during emergence from anaesthesia. (21) 3. M. Aho et al in Anaesthesia and Analgesia published an article that intramuscularly given dexmedetomidine of 2.4 µ/kg 45 minutes before surgery attenuated hemodynamic and stress response to gynecologic laparoscopy. (22) 4. H.A.Mowafi et al in British Journal of Anaesthesia, 2008, published the effect of dexmedetomidine premedication on intra ocular pressure changes after scoline and intubation. They showed that dexmedtomidine 0.6µ/kg intravenous resulted in decrease in intraocular and mean arteriolar pressure in the study group. They concluded dexmedetomidine could be a beneficial adjunct in open globe injuries. (23) 5. Ahmed M Muktar et al, Department of medicine, Cairo University studied the use of dexmedetomidine in paediatric cardiac surgery. They concluded dexmedetomidine attenuated increase in heart rate , blood pressure, cortisol and catecholamine concentration in paediatric patients undergoing open heart surgeries. (24) 6. Fredi Menda et al, Department of Anaesthesia, yeditepe university, Turkey, published in annals of cardiac Anaesthesia, about the effect of using dexmedetomidine as an adjunct

12**to attenuate hemodynamic response to endotracheal intubation in patients**

undergoing Fast trach **CABG.**

The study concluded

12**dexmedetomidine can** be **safely used to attenuate the hemodynamic response to endotracheal intubation in patients undergoing myocardial** revescularisation **receiving**β **blockers.**

(25)

13**AIM OF THE STUDY To** study **the effect of** dexmedetomidine in attenuating **the** arterial **pressure**

increase due to pneumoperitoneum in patients posted for elective laparoscopic cholecystectomy STUDY DESIGN It is single blinded randomised study done at Kilpauk Medical College/Government Royapettah Hospital PATIENT SELECTION: 40 patients of ASA 1 & 2 of both sex undergoing elective laparoscopic cholecystectomy are selected. GROUP: Group A: 20 patients receiving normal saline IV infusion 10 minutes before pneumoperitoneum Group B: 20 patients receiving IV dexmedetomidine (0.5µ/kg IV bolus followed by IV infusion of 0.5 µ /kg/hr) 10 minutes before pneumoperitoneum INCLUSION CRITERA ‣ ASA 1 &2 ‣ 18 to 60 years ‣ Both sex ‣ Elective cholecystectomy ‣ Without any co morbid condition ‣ Undergoing general anaesthesia EXCLUSION CRITERIA: ‣ Patient on any drug treatment which may interfere with dexmedetomidine ‣

4**Hypertension ‣ Diabetes mellitus ‣ Cardiovascular & kidney disease ‣ Acute** cholecystectomy ‣ Endocrine **or metabolic**

diseases ‣ Autonomic neuropathy ‣ Patients on chronic β blocker therapy MONITORING: ‣ Pulse oximetry ‣ NIBP ‣ ECG ‣ Et CO2 ‣ Airway pressure monitoring (PIP and mean pressure) ‣ Intra abdominal pressure (maintained around 12 mm of Hg) ‣ Urine output monitoring ‣ Temperature monitoring CONDUCT OF STUDY; After ascertaining the inclusion criteria preoperative investigations were recorded which included complete hemogram, blood sugar, urea, creatinine, serum electrolytes, blood grouping, blood coagulation tests, urine routine, chest X-ray and ECG. Preoperative instructions: ? All patients are explained about the study and written informed consent obtained. ? Patients are advised a 6 hour period of absolute fasting. ? All patients receive an antacid prophylaxis of injection ranitidine 50 mg IV and injection ondansetron 8 mg IV on the morning of surgery. ? All the patients are premedicated with injection glycopyrrolate 0.2 mg IM one hour before surgery. ? 40 patients are randomized

6**into two groups (group A and group B).**

Conduct of anaesthesia: ? After shifting the patients to operation theatre patients are connected to ECG, pulse oximetry, NIBP, and EtCO2 monitors. ? All patients are started with ringer lactate at 75 ml/hr. ? All patient given fentanyl 2µg/kg IV and pre oxygenated with 100% oxygen for 3 – 5 minutes. ? In all the patients

4**trachea was intubated after induction of anaesthesia with**

propofol 1.5

25**-2 mg/kg and vecuronium 0.1 mg/kg. ? Anaesthesia maintained with** 1 **.5-**

2% sevoflurane and 4:2 N2O/O2 at 6 litres/ minute. ?

22**After induction of general anaesthesia and**

10 minutes before creation of CO 2 pneumoperitoneum study group (group B) received IV dexmedetomidine 0.5

18**µg/kg** bolus **dose over 10 minutes** followed by **0.** 5µ **/kg/min infusion**

and control group (group A) received normal saline at same infusion rate. In both the groups infusion was continued till dissection of gall bladder was complete. ?

13**Arterial pressure and heart rate** are **measured before induction,**

pre pneumoperitoneum, at

4**pneumoperitoneum(P0), at 5** min , **10** min, **20** min, **30 min after pneumoperitoneum** and **post surgery.**

? Serum noradrenaline samples are taken pre pneumperitoneum and at 10 minute pneumoperitoneum. ? After completion of surgery, pneumoperitoneum deflated slowly and after the patient had adequate

respiratory attempts patient reversed with glycopyrrolate and neostigmine IV. ? Adequate oral suctioning done and the patients are extubated. ? After adequate recovery from general anaesthesia, patients were shifted to recovery room where they remained and observed until there was complete recovery from general anaesthesia for 2 hours. Noradrenaline assay ? Serum samples are taken in both plain tube and EDTA tubs and immediately transfered to the laboratory. ? Assay done with ECLIA using Elecsys 2010 system DEFINITION OF VARIABLES: ‣ Preoperative values of pulse

8rate, systolic, diastolic and mean blood pressures were recorded

read as outside theatre. ‣ Patients were preoxygenated and the reading of pulse

8rate, systolic, diastolic and mean blood pressures were recorded and

was read as preoperative. ‣ Patients were intubated and the reading of pulse

8rate, systolic, diastolic and mean blood pressures were recorded and

was read as prepneumoperitoneum. ‣ After induction of pneumoperitoneum (intra abdominal pressure reaching 12 mm of Hg) reading of pulse

8rate, systolic, diastolic and mean blood pressures were recorded and

was read as P0. ‣ From the induction of pneumoperitoneum, pulse

8rate, systolic, diastolic and mean blood pressures were recorded

at 5 th minute and was read as P5. ‣ From the induction of pneumoperitoneum, pulse

8rate, systolic, diastolic and mean blood pressures were recorded

at 10 th minute and was read as P10. ‣ From the induction of pneumoperitoneum, pulse

8rate, systolic, diastolic and mean blood pressures were recorded

at 20 th minute and was read as P20. ‣ From the induction of pneumoperitoneum, pulse

8rate, systolic, diastolic and mean blood pressures were recorded

at 30 th minute and was read as P30. ‣ After completion of the surgery patient extubated and pulse

8rate, systolic, diastolic and mean blood pressures were recorded and

was read as post surgery . STATISTICAL ANALYSIS: ‣ It's a randomized controlled clinical study ‣ Variables were analysed with Student't' test ‣ Variables like age, sex, weight, height were compared using Levene's test for equality of variance ‣ Sample size obtained according to previous background study ‣

14'p' value less than 0.05 was taken as significant OBSERVATION & RESULTS In this study a total of

40 patients were studied in which 20

13patients in the control (group A) and 20 in the study group (group B). The

demographic parameters like age distribution, weight of the patient(kg), height of the patient (cm), and other parameters like duration of anaesthesia, duration of surgery, preoperative pulse rate,

21systolic, diastolic and mean arterial pressure were compared between the two groups(

6group A & group B) and there was no statistical difference between the two groups(p > 0.05).

DEMOGRAPHIC AND OTHER PARAMETERS VARIABLE CONTROL STUDY P VALUE (GROUP A) (GROUP B) AGE 48.2 ±5 49.1±4 0.607 SEX M/F 8/12 9/11 0.704 WEIGHT (kg) 77.8±8 70.2±6 0.329 HEIGHT (cm) 163.7±7 165±7 0.509 DURATION OF SURGERY DURATION OF ANAESTHESIA PREOP PULSE RATE PREOP SYSTOLIC BP PREOP DIASTOLIC BP PREOP MEAN BP 39.3±4 39.9±4 0.620 67.5±6 69.2±4 0.340 87.8±10 86.2±4 0.510 107.2±11 102.9±18 0.420 63.6±8 67.3±9 0.205 78.1±9 81.9±9 0.220 50 Age 45 age 40 control Study Chart-1 Age distribution between two groups Sex Distribution Control group Study group female 60% male 40% female 55% male 45% Chart-2 Sex distribution in both groups 167 164 161 158 155 152 149 146 143 140 control Height Study height Chart-3 Height (in cms) between both groups 72 Weight 70 68 66 64 weight 62 60 control Study Chart-4 Weight (in

kg) between both groups 80 70 control Study 67.5 69.2 60 50 40 39.25 39.9 30 20 10 0 dur of sx dur of Ax Chart-5 Duration of surgery and duration of anaesthesia are comparable between two groups. 120 100 80 60 87.85 86.15 107.25 100.95 63.65 67.3 control Study 78.1 81.9 40 20 0 PR Pre op sys Pre op dia Preop mean Preop Chart-6 Preoperative pulse rate,

> 21**systolic, diastolic and mean blood pressure** are comparable **between** two **groups.**

PULSE RATE VARIABLE CONTROL STUDY P VALUE (GROUP A) (GROUP B) MEAN P 0 89.2 77.4 0.000 MEAN P5 85.4 75.0 0.000 MEAN P 10 87.0 73.8 0.000 MEAN P 20 88.0 72.1 0.000 MEAN P 30 84.4 75.2 0.003 MEAN POST SURGERY 88.5 79.6 0.003 P value <0.05 - significant Test method – student t test The pulse rate is significantly low in the study group (group B) than the control group (group A) during the period of pneumoperitoneum at 0 min (77 VS 89), 5 th min (75 vs 85), 10 th min(73 vs 87), 20 th min (88 vs72) and 30 th min (75 vs 84) and also post surgery (79 vs 88). (chart -7) 100.0 90.0 80.0 70.0 60.0 50.0 Control

> 17**Study 40.0 30.0 20.0 10.0 0.0**

PR P0 PR P5 PR P10 PR P20 PR P30 PR POST SX Chart-7 Bar diagram shows heart rate is significantly lower (p value <

> 6**0.05) in** study **group than the control group** at all point **of**

time. SYSTOLIC BLOOD PRESSURE VARIABLE CONTROL STUDY P VALUE

> 6**(GROUP A) (GROUP B)** SYSYTOLIC **P 0**

109.2 103.8 0.003 SYSTOLIC P5 119.3 108.5 0.000 SYSTOLIC P 10 128.3 110.8 0.000 SYSTOLIC P 20 123.9 115.4 0.000 SYSTOLIC P 30 128.5 120.9 0.000 SYSTOLIC POST SURGERY 130.5 123.7 0.001 P value <0.05 - significant Test method – student t test The systolic blood pressure is significantly low in the study group (group B) than the control group (group A) during the period of pneumoperitoneum at 0 min (103 vs 109), 5 th min (108 vs 119), 10 th min(110 vs 128), 20 th min (115 vs 123) and 30 th min (120 vs 128) and also post surgery(123 vs 130). (chart- 8) 140.0 120.0 100.0 80.0 60.0 Control Study 40.0 20.0 0.0 sys P0 sys P5 sys P10 sys P20 sys P30 post sx Chart-8 Bar diagram shows systolic blood pressure is significantly lower (p value <

> 6**0.05) in** study **group than the control group** at all point **of**

time. DIASTOLIC BLOOD PRESSURE VARIABLE CONTROL STUDY P VALUE

6**(GROUP A) (GROUP B)** DIASTOLIC **P 0**

80.3 75.0 0.000 DIASTOLIC P5 84.2 76.2 0.000 DIASTOLIC P 10 91.3 76.9 0.000 DIASTOLIC P 20 89.8 81.2 0.000 DIASTOLIC P 30 86.9 80.1 0.003 DIASTOLIC POST SURGERY 82.8 74.7 0.001 P value <0.05 - significant Test method – student t test The diastolic blood pressure is significantly low in the study group (group B) than the control group (group A) during the period of pneumoperitoneum at 0 min (75 vs 80), 5 th min (76 vs 84), 10 th min(76 vs 91), 20 th min (81 vs 86) and 30 th min (80 vs 86) and also post surgery(74 vs 82). (chart-9) 100.0 90.0 80.0 70.0 60.0 50.0 Control

17**Study 40.0 30.0 20.0 10.0 0.0**

dia P0 dia P5 dia P10 dia P20 dia P30 dia post sx Chart-9 Bar diagram shows diastolic blood pressure is significantly lower (p value <

6**0.05) in** study **group than the control group** at all point **of**

time. MEAN BLOOD PRESSURE VARIABLE CONTROL STUDY P VALUE

6**(GROUP A) (GROUP B)** MEAN **P 0**

92.9 85.7 0.000 MEAN P5 98.5 87.5 0.000 MEAN P 10 104.9 89.3 0.000 MEAN P 20 102.8 94.3 0.000 MEAN P 30 99.0 94.5 0.003 MEAN POST SURGERY 94.7 84.7 0.001 P value <0.05 - significant Test method – student t test The

28**mean blood pressure** is **significantly** low **in the study group** (group B) **than the control group**

(group A) during the period of pneumoperitoneum at 0 min (85 VS 92), 5 th min (87 VS 98), 10 th min(89 VS 104), 20 th min (94 VS 102) and 30 th min (94 VS 99) and also post surgery(84 VS 94). (chart-10) 120.0 100.0 80.0 60.0 Control Study 40.0 20.0 0.0 mean P0 mean P5 mean P10 mean P20 mean P30 mean post sx Chart-10 Bar diagram shows mean arterial pressure is significantly lower (p value <

6**0.05) in** study **group than the control group** at all point **of**

time. SERUM NORADRENALINE VALUES VARIABLE CONTROL STUDY P VALUE (GROUP A) (GROUP B) PRE PNEUMO 200.5 194.8 0.367 PERITONEUM 10 MIN PNEUMO 481.0 302.3 0.000 PERITONEUM P value <0.05 significant The nor adrenaline values are not significant between the

> 6**control group (group A)** and the study **group (group B)**

before pneumoperitoneum (200.5 vs 194.8 pg/ml). But the values between the

> 6**control group (group A)** and the study **group (group B)**

taken at 10 minute pneumoperitoneum are very much significant (481.0 vs 302.3 pg/ml) suggesting attenuation of hemodynamic response arising due to CO 2 pneumoperitoneum. (chart -11) 600.0 Control Study Nor adrenaline levels 500.0 481.0 400.0 300.0 200.0 200.5 194.8 302.3 100.0 0.0 prepneumo_NA Time 10_min_NA Chart-11 Bar diagram shows that noradrenaline levels are higher in the control group after induction of pneumoperitoneum but there is significant lower levels in the study group after induction of pneumoperitoneum. DISCUSSION In this study neurohormonal hemodynamic response of dexmedetomidine in attenuating the arterial pressure increase is studied. The results obtained showed an effective attenuation of blood pressure and

> 20**heart rate in patients who received dexmedetomidine** as **compared** to the **patients who received**

normal saline. The study also showed that dexmedetomidine effectively suppressed the noradrenaline release due to pneumoperitoneum in the

> 20**patients who received dexmedetomidine** but not in **patients who received**

normal saline. Thus proving that dexmedetomidine acts by suppressing the central sympathetic outflow (sympatholytic) there by suppressing the hemodynamic changes induced by the CO 2 pneumoperitoneum. Many studies have been done on laparoscopic surgery and highlighted hemodynamic changes during pneumoperitoneum and also proved by endocrine co relates the reason for the pneumoperitoneal response. The landmark study which was conducted about the hemodynamic response of laparoscopy with CO 2 pneumoperitoneum by Jean L. Loris et al which was published in JACC 1998, (26) showed that there is

> 3**significant reduction of cardiac output and** increase **in mean arterial pressure and systemic**

vascular resistance.

4**In the present study we** also **observed that systolic,** diastolic **and** mean **arterial** pressure **increased abruptly after** induction of **pneumoperitoneum and**

this response

4**sustained during the entire pneumoperitoneum period in the control group** (group A) **as** observed by the **previous**

studies. Dexmedetomidine being a anxiolytic, sedative and sympatholytic effectively suppresses the stress response in various situations. In the study by Poonam S.Ghodki et al in journal of Anaesthesiology clinical pharmacology 2012, (20) studied dexmedetomidine as an anaesthetic adjuvant in laparoscopic surgery and they concluded dexmedetomidine is an effective adjunct without the fear of awareness under anaesthesia and resulted in 62.5% reduction in induction dose of propofol and 30% less end tidal isoflurane required. Similarly Clonidine which is congener of dexmedetomidine has been studied in attenuating the stress response in laparoscopic surgeries. In the study by Jean L. Loris et al (26) that found that Clonidine effectively attenuated the stress response due to pneumoperitoneum. Similarly in our study we found that in the dexmedetomidine group (group B) hemodynamic

4**responses to the** induction **of pneumoperitoneum were effectively blunted and**

the heart rate and blood pressure levels

4**when compared** to **the control group (group**

A). Even though study conducted by D.Jee et al, published in British Journal of Anaesthesia 2009, (27) studied the effect of magnesium sulphate on pneumoperitoneum response showed that there is no change in heart rate in the magnesium group when compare to control group. But Jean L,Loris showed that Clonidine significantly reduced both heart rate and blood pressure. Our study reports also show the same that dexmedetomidine attenuates both heart rate and blood pressure significantly. ENDOCRINE CORRELATES OF LAPAROSCOPY Loris et al (26) in his study showed the endocrine correlation of pneumoperitoneal response. The study showed that the reason the increase in the peripheral vascular response is due to increase in vasopressin and catecholamines levels. More precisely the study showed that vasopressin levels correlated

3**closely with changes in** peripheral vascular response. **Induction of**

pneumoperitoneum causes

3**rapid and marked release of vasopressin**

and it well co related

3**with changes in** intra abdominal **pressure , intrathoracic and**

right atrial pressure. The reason for release of vasopressin is not clearly known and it may be probably due to mechanical stimulation of peritoneal receptors. Catecholamines particularly noradrenaline which was released during pneumoperitoneum also contributes to increase in peripheral vascular resistance. The stimulus for the release of noradrenaline is not known. The reason may be due to surgical stress induced by the pneumooeritoneum in laparoscopy. Loris et al also studied the effect of Clonidine on laparoscopy and showed that Clonidine effectively attenuated the release of catecholamines and thereby decresing the afterload. But study didn't showed correlation with vasopressin. Vasopressin and cortisol levels were same in both the groups. Since dexmedetomidine has similar mode of action as Clonidine we assumed that vasopressin levels donot have much effect, so we selected to study nor adrenaline levels before and after pneumoperitoneum. In both study group and the control group, we studied the noradrenlaine levels before pneumoperitoneum and 10 minutes after induction of pneumoperitoneum. In the control group (group A) the 10 minutes serum noradrenaline values were significantly higher than the pre pneumoperitneal values. This is similar to the studies conducted by Loris et al, (26) Lee et al, (27) Jens fromholt Larsen et al (29) on hemodynamic response of pneumoperitoneum. In the study group (group B), where patients received 0.5 µg/kg of dexmedetomidine as bolus dose over ten minutes before pneumoperitoneum, the noradrenaline levels taken 10 minutes after induction of pneumoperitoneum

6**were significantly** not **increased when compared with the pre**

pneumoperitoneal values. Thus our study proved that the attenuation of arterial pressures by dexmedetomidine is due to suppression of catecholamines levels specifically noradrenaline by its central sympatholytic action. This is similar to studies conducted with dexmedetomidine by Pekka Talke et al (21) in attenuation of stress response by dexmedetomidine in vascular surgeries, and H.A.Mowafi et al (23) in attenuation of ocular pressure changes by dexmedetomidine.

4**Prolonged intraoperative increases of 20 mm** of **Hg or more in mean arterial pressure**

can cause significant implications in cardiovascular system. It can cause increase

> 4**incidence of myocardial** ischemia, **infarction and death.**

So by attenuating these responses in laparoscopy surgeries, dexmedetomidine may be of immense use in decreasing the morbidity in high risk cardiac patients. Our study concludes that dexmedetomidine can definitely be used for the attenuation of the hemodynamic responses arising due to CO2 pneumoperitoneum. SUMMARY In our

> 4**study, ‣ We observed, that** the **systolic,** diastolic **and** mean **arterial** pressure **increased abruptly after** induction of **pneumoperitoneum and**

this response

> 4**sustained during the entire pneumoperitoneum period in the control group(**

group A). ‣ We observed that in the dexmedetomidine group(group B) hemodynamic

> 4**responses to the** induction **of pneumoperitoneum were effectively blunted and**

the heart rate and blood pressure levels when

> 6**compared to the control group(** group **A). ‣ In**

the control group (group A) the 10 minute serum noradrenaline values were significantly higher than the pre pneumoperitoneal values suggesting that all these hemodynamic changes are due to release of catecholamines. ‣ In the study group (group B), the noradrenaline levels taken 10 minutes after induction of pneumoperitoneum

> 6**were significantly** not **increased when compared with the pre**

pneumoperitoneal values suggesting that dexmedetomidine effectively suppressed the hemodynamic responses by its central sympatholytic action. CONCLUSION We conclude that intravenous administration of dexmedetomidine as an adjunct before induction of pneumoperitoneum in laparoscopic cholecyctectomy effectively attenuates the arterial pressure increase due to pneumoperitoneal

10response. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78

MASTER CHART – CONTROL GROUP

name	sex	age	height	weight	dur of sx	dur of Ax	PR Pre op	sys Pre op	dia Preop	mean Preop	PR P0	sys P0	dia P0	mean P0
rajammal	F	48	156	53	34	57	86	111	74	84	70	103	78	84
sekar	M	50	167	68	37	58	84	112	76	85	74	104	78	84
antony	M	42	170	70	40	62	84	123	74	92	72	103	78	84
kumari	F	40	158	66	43	70	86	123	74	92	84	103	78	84
arokiaraj	M	52	165	75	45	75	86	123	74	92	84	106	74	84
ramkumar	M	56	166	72	42	73	90	127	71	94	72	103	78	84
darun	M	54	174	78	36	60	76	97	54	68	88	102	70	86
durgadevi	F	53	160	62	32	66	92	102	57	71	91	101	70	88
renuka	F	38	155	65	30	54	67	93	61	75	90	104	77	89
rajalakshmi	F	42	159	58	37	72	99	117	69	84	104	120	77	90
ellappan	M	48	160	64	38	69	102	100	58	70	104	106	70	86
akbar	M	47	169	65	40	77	76	97	54	68	88	102	70	86
santhakumari	F	54	154	59	42	74	92	100	61	76	93	134	90	104
mary	F	50	162	67	44	69	102	100	59	71	102	105	72	85
anburaj	M	52	172	80	45	74	76	98	54	69	89	100	68	86
sankari	F	56	158	59	42	72	87	121	76	90	92	112	78	88
swaminathan	M	47	171	84	37	64	102	102	58	72	104	106	70	86
rajiv	M	45	178	80	38	66	102	100	58	70	104	106	70	86
vasudevan	M	39	165	70	40	68	76	97	54	68	88	102	70	86
yuvarani	F	51	155	61	43	70	92	102	57	71	91	101	70	88

MASTER CHART – CONTROL GROUP

PR P5	sys P5	dia P5	mean P5	PR P10	sys P10	dia P10	mean P10	PR P20	sys P20	dia P20	mean P20	PR P30	sys P30	dia P30	mean P30		prepneumo NA	10 min NA
81	126	84	106	76	134	90	107	76	128	85	100	70	114	76	92		220	510
80	126	86	106	78	134	90	107	78	126	85	100	75	116	70	93		197	474
81	128	86	104	77	137	91	108	71	129	87	100	70	114	76	92		178	460
81	126	84	104	78	135	90	108	79	128	87	100	70	114	76	92		210	490
80	126	84	104	79	134	90	108	80	128	87	100	74	116	78	92		170	446
81	128	86	104	77	137	91	108	71	129	86	100	70	113	86	94		190	464
80	103	78	88	79	118	86	94	90	114	84	100	81	116	86	99		226	506
93	119	84	92	89	125	86	93	94	123	90	96	90	117	84	92		184	478
78	102	73	88	79	119	85	97	77	110	80	94	79	104	75	89		204	494
93	131	97	112	102	134	97	111	100	134	92	105	97	137	94	107		217	507
93	120	85	97	103	132	100	116	98	130	104	115	98	133	100	112		182	490
80	103	78	88	79	118	86	94	90	114	84	100	81	116	86	99		196	471
89	131	97	112	102	134	102	115	102	114	84	100	100	116	84	98		211	504
94	120	85	97	101	131	103	117	98	132	104	117	98	133	100	112		230	522
80	103	78	88	79	105	76	89	88	114	84	100	81	118	86	101		180	450
84	128	86	104	88	132	90	106	88	127	90	103	86	124	90	100		206	510
93	123	85	98	103	132	100	116	98	130	104	115	98	133	100	112		199	484
93	120	85	97	103	132	100	116	98	130	104	115	98	133	100	112		211	450
80	103	78	88	79	118	86	94	90	114	84	100	81	116	86	99		172	420
93	119	84	92	89	125	86	93	94	123	90	96	90	117	84	92		226	490

MASTER CHART – STUDY GROUP

name	sex	age	height	weight	dur of sx	dur of Ax	PR Pre op	sys Pre op	dia Preop	mean Preop	PR P0	sys P0	dia P0	mean P0
santhakumar	M	49	161	65	43	72	78	97	54	68	80	100	68	86
ramadevi	F	53	153	63	42	65	79	98	54	68	80	100	68	86
saroja	F	56	159	68	45	68	84	112	76	85	74	104	74	82
lakshmi	F	55	160	72	39	67	86	111	74	84	70	103	78	84
shenbagavalli	F	43	155	64	35	72	76	96	54	68	74	100	68	84
kumar	M	47	175	80	32	66	88	124	74	92	78	103	76	83
hariharan	M	39	174	78	37	64	92	100	61	76	87	103	72	84
ashokan	M	47	172	72	45	74	84	97	52	68	74	102	70	86
ambika	F	46	165	70	36	67	90	123	74	92	84	106	74	84
anbukarasu	M	50	168	68	42	75	94	125	72	92	84	103	78	84
malar	F	52	179	82	42	74	82	123	74	92	72	102	78	94
senthilnathan	M	54	166	72	36	66	90	11	74	84	84	105	78	85
kanchana	F	53	157	64	35	65	88	123	71	90	72	105	78	86
srinivasan	M	48	164	70	40	70	84	112	76	85	74	104	74	82
krishnan	M	46	173	77	38	61	92	100	61	76	80	116	84	98
padmavathy	F	45	170	73	45	76	86	112	74	84	72	103	78	84
babu	M	56	166	74	42	73	88	124	74	92	78	103	76	83
ramoorthy	M	51	163	66	41	69	84	97	52	68	74	104	70	87
sudharshan	M	43	167	71	46	75	90	11	74	84	84	105	78	85
kannagidevi	F	48	157	54	37	65	88	123	71	90	72	105	80	86

MASTER CHART – STUSY GROUP

PR P5	sys P5	dia P5	mean P5	PR P10	sys P10	dia P10	mean P10	PR P20	sys P20	dia P20	mean P20	PR P30	sys P30	dia P30	mean P30		prepneumo NA	10 min NA
70	103	78	88	70	104	76	89	76	110	84	98	80	114	84	100		199	304
80	104	78	89	84	104	70	88	76	110	84	98	80	114	86	101		211	302
72	108	76	84	70	106	78	85	70	114	76	92	80	128	85	104		187	284
72	108	72	86	76	106	76	84	74	114	76	92	80	116	76	93		178	302
76	103	78	88	79	105	76	89	80	112	84	98	81	118	86	91		224	310
76	110	74	84	72	128	74	94	77	113	86	94	78	129	86	100		198	320
80	106	78	90	79	103	78	88	78	114	84	100	80	116	84	98		190	292
72	103	78	88	68	106	80	90	68	110	76	86	66	114	82	99		234	422
70	108	72	83	68	107	74	84	68	116	78	92	66	118	78	92		164	278
81	126	84	104	76	125	70	92	74	128	87	100	70	114	76	92		172	270
81	110	72	86	70	114	76	92	69	112	73	89	68	110	73	89		204	303
78	112	72	84	76	110	72	84	74	114	85	92	74	126	84	106		222	307
70	103	78	84	72	113	86	94	60	120	86	98	67	128	56	104		193	289
72	108	76	84	70	106	78	85	70	114	77	93	89	128	85	107		187	294
82	114	84	100	82	113	86	100	75	126	78	98	79	131	97	112		178	278
72	109	72	86	75	106	76	84	74	120	76	92	80	116	76	93		167	311
76	110	74	84	72	128	74	94	77	113	86	94	78	129	86	100		218	298
72	103	78	83	68	108	80	92	68	112	76	87	66	114	82	99		180	298
78	114	72	86	76	110	72	84	74	116	85	94	74	126	84	106		217	300
70	108	78	88	72	114	86	94	60	120	86	98	67	128	56	104		172	284